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Research Plan for Arsenic in Drinking Water

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Board of Scientific Counselors (BOSC)
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INTRODUCTION

Purpose

This research plan addresses opportunities to enhance the scientific basis for understanding the exposures and health risks associated with arsenic in drinking water. Better understanding of arsenic health risks will provide an improved science base for arsenic risk assessment and regulatory decisions in the United States. This research plan is expected to be of interest to scientists, risk assessors and policy makers in government, industry, and academia as well as members of the public interested in arsenic exposure. The issue of arsenic research needs and the basis for current risk assessments have been the subject of several reviews and expert panels (AWWARF, 1995; U.S. EPA, 1988a, 1991, 1992, 1996). Therefore, this document stresses the implications of recent research findings and emphasizes identification of key strengths and sources of uncertainty and variability[1] in the arsenic risk assessment. This document will also explain how information gained through research can

- impact the methods used in new investigations to assess the risks of arsenic, and
- support or suggest changes in the assumptions and methods used in arsenic risk assessments, e.g., generating ~~or~~ arsenic-specific information for use in place of standard default assumptions.

The risk assessment/risk management paradigm was chosen as the format for the strategy because risk assessment provides a systematic approach to analyze sources of scientific uncertainty and variability which can influence research directions more effectively (NRC, 1994). The risk assessment/risk management paradigm involves four types of scientific analyses followed by risk management decisions. The risk assessment analyses consists of *hazard identification, dose-response assessment, exposure assessment* and *risk characterization* (NRC, 1983). Hazard identification involves descriptions of the potential adverse effects (e.g., short-term illness, cancer, reproductive effects) that might occur due to exposure to the environmental stressor (e.g. arsenic). Dose-response assessment determines the toxicity or potency of the stressor by describing the

[1] The terms uncertainty and variability, as used here, have distinct meanings (NRC, 1994). Uncertainty refers to gaps in knowledge, and variability to interindividual differences (heterogeneity) in both exposure and personal dose–response relationships (susceptibility).

quantitative relationship between the amount of exposure to a stressor and the extent of injury or disease. Exposure assessment describes the nature and size of the populations exposed to a stressor and the magnitude and duration of exposure. Exposure assessment also includes descriptions of the pathways (e.g. air, water, food supply) by which the stressor travels through the environment along with the potential routes of exposure (oral, dermal, or inhalation). Risk characterization uses the data collected from the three preceding analyses which are integrated together to convey the overall conclusions about potential risk, as well as the rationale, strengths and limitations of the conclusions. The risk characterization provides an estimate of the likelihood that individuals in a population will experience any of the adverse effects associated with the stressor, under known or expected conditions of exposure. Risk management decisions for drinking water involve setting maximum contaminant levels (MCLs), based on minimizing adverse health effects considering the available technologies. In the context of this strategy, risk management research involves identifying treatment technology options and evaluating their performance, cost, and effectiveness.

This Arsenic Research Plan addresses the protection of human health, especially the research needed to implement the 1996 Safe Drinking Water Act Amendments. It is intended to serve as a blueprint that will be discussed with parties interested in addressing key strengths and uncertainties in the arsenic risk assessment. The research needs are broader than those that EPA can address alone, and it is anticipated that other entities will be involved in conducting some of the needed research.

Background on Arsenic

Arsenic occurs widely in the earth's crust and is a natural contaminant of water. Elevated levels of arsenic in water and soil can be found in certain areas of the country as a result of leaching from rock into ground water and possible geothermal activity, depending on the geologic make-up of the area. In addition, nonferrous mining and smelting operations, refining operations, wood preservative use, contaminated pesticide manufacturing sites, and past use of pesticides on crops (e.g., cotton) may add to elevated concentrations of arsenic in water and soils. Humans are

exposed to arsenic in a variety of forms from sources such as food and water. Arsenic has also been used for medicinal purposes.

Arsenic is a transitional, reactive element that forms complexes with other metals, as well as carbon and oxygen (Gorby, 1994). There are three biologically important arsenic valence states: elemental arsenic As(0), arsenite As(III) and arsenate As(V). Arsine gas is considered the most toxic; inorganic arsenic compounds are generally considered to be more toxic than organic arsenic compounds. Elemental arsenic is the least toxic. The inorganic arsenicals are the predominant forms found in water.

Although the general toxicity of arsenic is widely known through poisoning incidents and its medical use, epidemiological reports of arsenic-related cancers in Taiwan and other populations have raised public health concerns about effects arising from chronic exposure. In Taiwan, an association between arsenic levels in drinking water and increased skin cancers in the exposed populations was observed (Tseng et al. 1968, and Tseng, 1977). Further evaluation of this study determined an increased risk of internal cancers as well (Chen et al. 1986). Effects other than cancer were also noted in this study. These include effects on the peripheral vasculature leading to Blackfoot's disease and noncancerous skin lesions such as altered pigmentation and skin thickening (hyperkeratosis). Animal studies suggest the possibility of other non-cancer effects occurring under certain conditions of exposure.

Regulatory Background

The authorities and responsibilities of the U.S. Environmental Protection Agency are mandated primarily by twelve major environmental statutes. These statutes direct EPA to perform a wide variety of activities with the underlying goal of protecting human health and the environment. This research strategy for arsenic specifically emphasizes research issues related to arsenic in drinking water. Therefore, the discussion in this section will focus on mandates under the Safe Drinking Water Act (SDWA), with some consideration of other statutes affected by the SDWA.

The Safe Drinking Water Act mandates that EPA identify and regulate drinking water contaminants that may have an adverse human health effect and that are known or anticipated to

occur in public water systems. As described above, arsenic meets these two criteria. EPA's drinking water standard, or maximum contaminant level (MCL), under SDWA is 50 µg/l for arsenic. This level was developed in 1942 by the Public Health Service and was not based on risk assessment methodology. Since that time, revision of the drinking water standard has been considered a number of times, but no change was made. In February, 1995, OW decided to delay proposals for the revision of the arsenic MCL pending additional health research to reduce uncertainties and to conduct research on arsenic removed by small system treatment technologies. The SDWA Amendments of 1996 require the development of an arsenic research strategy within 180 days of enactment, a proposal to revise the MCL by January 2000, and a final rule by January 2001.

The Office of Water (OW) has established guidance for arsenic under the Clean Water Act (CWA). Under the CWA, a human health water quality criterion for arsenic was established at 0.018 µg/l. This intake level is equal to a one in one million (10^{-6}) increase in the probability of cancer risk for arsenic exposures. Water quality criteria are used as guidance to States in establishing surface water quality standards and discharge limits for effluents.

Having two very different criteria for arsenic (0.018 µg/l in ambient water vs. 50 µg/l in drinking water) to protect human health exposures to drinking water is very confusing to the public. These different values have been difficult to explain, defend, and implement in EPA and State programs.

Treatment efficiency is a major concern for risk managers since removal of arsenic from water and soil can cost billions of dollars. Previous EPA draft estimates indicate that, depending on the revised MCL, national cost estimates for implementation range from $140 million to $6.2 billion, for MCLs ranging from 20 down to 5 µg/l (cost estimates will be revised based on analyses to be conducted pursuant to the new SDWAA provisions). Treatment costs are of particular concern for small communities, since costs are spread among fewer households. Thus, there has been and continues to be considerable scrutiny placed on the health effects database and resulting risk assessment for ingested arsenic which serves as guidance for Agency decision-making. In this respect, the uncertainty and interpretation differences in the risk assessment have made decisions difficult.

The arsenic risk assessment also has an impact on the Superfund program. Superfund requires that EPA respond to spills and other releases, or threatened releases, of identified hazardous substances and leaking hazardous waste dumps. The Superfund Amendments and Reauthorization Act of 1986 (SARA) requires that EPA prepare a list of at least 275 of the hazardous substances most commonly found at National Priority List sites; arsenic is a contaminant of concern at many Superfund sites. Furthermore, EPA is required to conduct the cleanups at the sites to levels that must assure protection of health and the environment, that is, specifically to meet the SDWA's recommended Maximum Contaminant Level Goals (MCLG) and the Clean Water Act's water quality criteria where appropriate.

Risk Management Decisions Required for Arsenic in Drinking Water

To meet the January 1, 2001, target for a final arsenic drinking water regulation, EPA's risk managers will rely on scientific results that are available, at the latest, by mid-1999. However, longer term research will also be important, because every 6 years EPA must review and revise, as appropriate, each national primary drinking water regulation promulgated. Key issues for risk management decision-making in developing a drinking water standard are described below.

1. Determine the Maximum Contaminant Level Goal (MCLG)

The MCLG is set at a level which will not result in adverse health effects, incorporating a margin of safety. In setting MCLGs, EPA's policy has been to distinguish between carcinogens and non-carcinogens as follows:

- For contaminants with adequate evidence of carcinogenicity via drinking water, considering weight of evidence, pharmacokinetics, potency and exposure, the MCLG is set at zero. Zero is chosen because it is assumed, in the absence of other data, that there is no threshold dose for carcinogenicity.
- For contaminants with limited or no evidence of carcinogenicity via water, the MCLG is based on non-cancer effects using the Reference Dose (RfD). The RfD is derived from a no or lowest adverse effect level identified from a sensitive endpoint of toxicity from a relevant human or animal study and adjusted to account for uncertainty of the findings with

regard to responses in the general population. Uncertainty factors are used to account for differences in response to toxicity within the human population and between humans and animals as well as other aspects of uncertainty with the study and database for that contaminant. The RfD is then adjusted for the bodyweight and average water consumption of the protected (or most sensitive) individual (adult or child). The resulting concentration is further adjusted by a relative source contribution factor to reflect exposure to that contaminant from a drinking water source (USEPA, 1994).

2. Determine the Maximum Contaminant Level (MCL)

An MCL is set as close to the MCLG as "feasible". The SDWA (section 1412(b)(5)) characterizes "feasible" as follows: "feasible with the use of best technology, treatment techniques, and other means which the Administrator finds available (taking costs into consideration) after examination for efficacy under field conditions and not solely under laboratory conditions".

- When setting an MCL, EPA defines best available technology (BAT) as feasible technologies for large public water systems, i.e., the MCL is set at the level which the BAT can achieve.
- Under the new SDWAA , EPA must also identify affordable technologies that will meet the MCL for small water systems in three population size categories:, 25-500; 501-3,300; and 3,301 - 10,000.
- EPA will establish a standard analytical method(s) to be used for compliance monitoring of the contaminant. In some cases, the detection limit (or practical quantification limit, PQL) that is feasible is what determines the MCL.

3. Determine if the benefits of the MCL will justify the compliance costs

The new SDWA Amendments expand upon the cost-benefit analysis previously required for drinking water regulations. Under the Amendments, EPA must

- Analyze quantifiable and nonquantifiable health risk reduction benefits likely to occur as a result of treatment of the contaminant and co-occurring contaminants, including health risk reduction benefits for infants, children, pregnant women, the elderly and ill.
- Analyze the quantifiable and nonquantifiable costs of compliance, including monitoring and treatment costs.
- Determine if the benefits justify the costs.

- If the benefits do not justify the costs, identify a higher MCL that maximizes health risk reduction benefits, where the costs are justified, unless the cost to large systems would justify the benefits. However, if the contaminant is found almost exclusively in small systems, a higher MCL can be established.

Scope of this Research Plan

The U.S. drinking water standard for arsenic (MCL) is based on policy recommendations developed before modern cancer and other health related data on arsenic became available. Even today regulation of arsenic in drinking water is controversial because of the uncertainties in the quantification of the health risks attributable to arsenic and the costs associated with treatment to remove arsenic from drinking water. However, legislation now requires rapid EPA action in order to issue a revised MCL for arsenic by 2001. The fundamental scientific basis for understanding the subchronic and chronic toxicities caused by arsenic (cancer, developmental problems, vascular problems, dermatologic problems, etc.) has also lagged behind empirical observation of these health problems further complicating the regulatory process.

In this context, EPA recognizes the need for both short term and longer term research on the risks posed by arsenic in drinking water. Research that can be conducted within a short time frame will best support current regulatory needs. Shorter term research is unlikely to produce fundamental changes in our understanding of arsenic health effects and risks. However, EPA believes that there is important research that can be accomplished in the near term to aid the Agency in making prudent risk management decisions. Beyond the immediate regulatory needs, it is evident that human exposures to arsenic will continue as a public health and risk assessment concern into the foreseeable future. Therefore, this plan also describes longer term research priorities that will improve our understanding of the toxicity of arsenic, lead to improvements in the risk assessment for arsenic, and serve as a basis for future risk management decisions.

This research plan describes the research that can contribute to the development of the

arsenic drinking water regulation, both in the near and longer terms.[2] Areas covered in the research plan include studies to:

- improve our qualitative and quantitative understanding of the human toxicity of arsenic;
- understand mechanisms of arsenic toxicity, using a variety of research tools, that may aid in quantitatively estimating the risks of arsenic at low doses;
- measure exposures of the US population to arsenic from various sources (particularly diet) thereby permitting better definition of cumulative exposures to arsenic; and
- refine treatment technologies that may better remove arsenic from water supplies.

Figure 1 depicts the risk assessment relationships of exposure assessment and effects assessment that are integrated into a final risk characterization. Figure 2 provides an overview of the arsenic research strategy and indicates how it will provide data for OW's use in developing drinking water regulations.

Prioritization Criteria

Decision-making criteria for use in priority-setting within this research program have been developed. These criteria are not listed in any order of importance and must be considered as a group when setting priorities. Through application of these criteria, resources will be allocated in the most effective and efficient manner.

- **Risk-Based Planning** - Research that addresses an element of the risk assessment paradigm and is designed to reduce the greatest uncertainties is of highest priority.
- **Policy Relevance** - The degree to which a research project addresses a specific need in the risk-management decision process.

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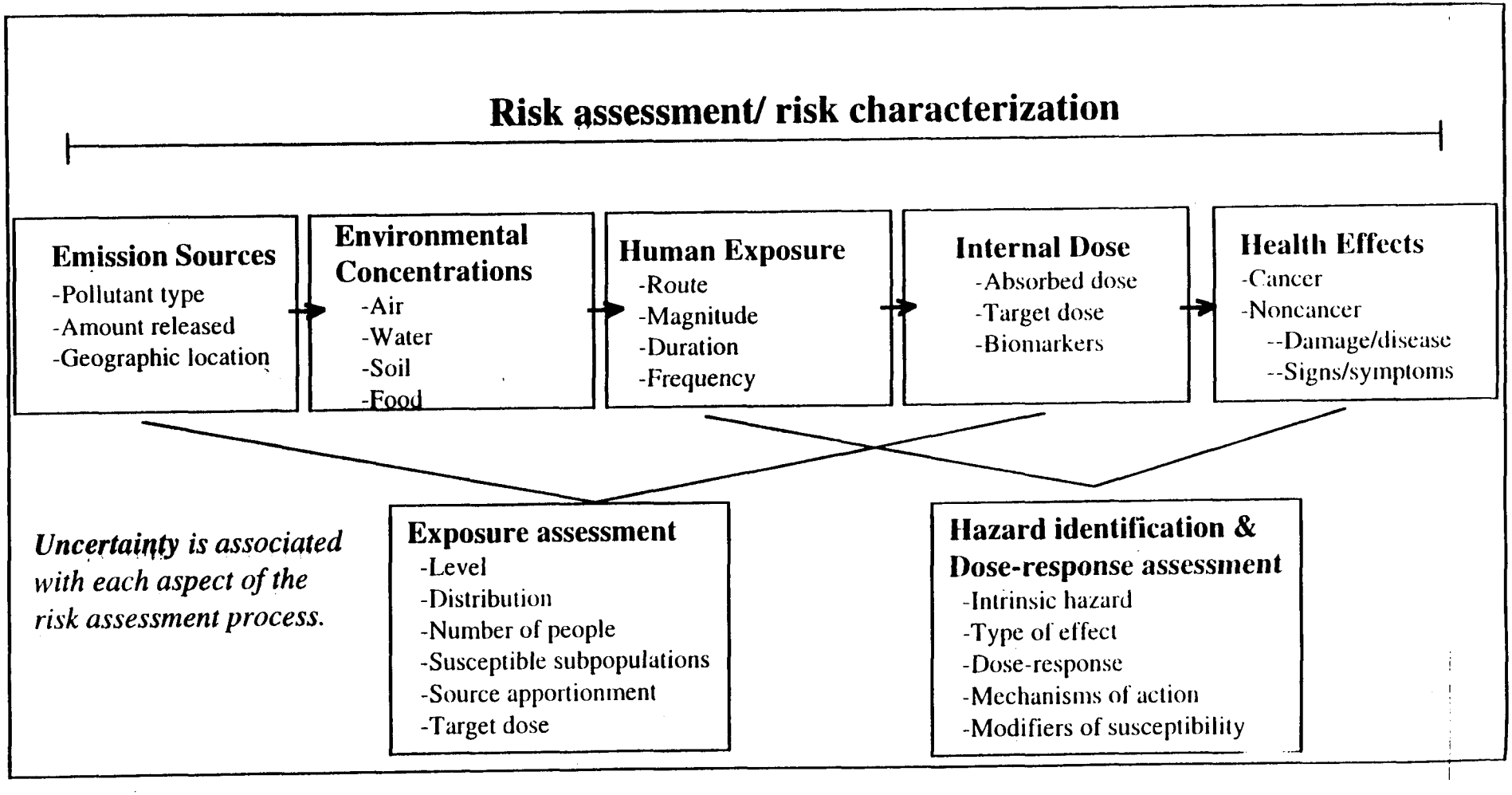
[2]However, this plan does not describe all the regulatory assessment and monitoring studies needed to support arsenic regulation. Such assessments would include studies of the prevalence of different levels of arsenic contamination in water supplies in the US and economic evaluations of regulatory costs. Such data collection and analysis falls outside the scope of research planning and is addressed directly by EPA's Office of Water.

- **Other Sources of Data** - It is important to determine whether research that will provide equivalent or complementary information is underway or planned elsewhere. A high priority will be given to projects that leverage resources within and/or outside the Agency.
- **Sequence of Research** - The value of some research, regardless of its priority ranking on other criteria, is dependent upon the completion of other work. Research that is dependent upon completion of otherwise equally ranked work will receive a lower priority.

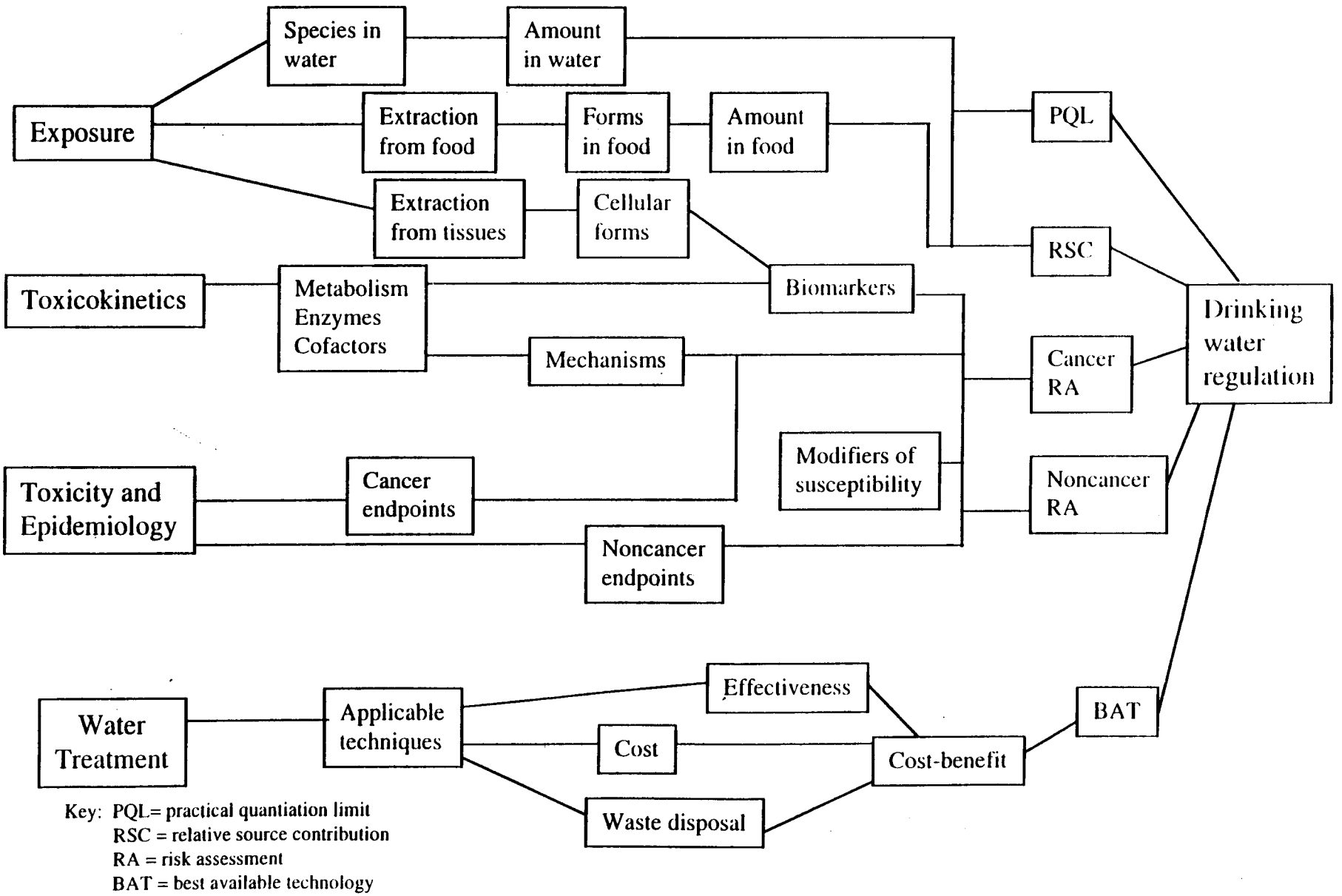
Within each proposed research area, the plan summarizes the primary focal area for the research, indicates whether the activity is targeted primarily toward the intramural or extramural (or both) components of the EPA research program, and the planning year in which the research is proposed to be undertaken. In some cases EPA expects the research to be conducted by other entities. While these tables also propose the research sequence, this strategic plan is likely to be refined as the program progresses and new research results emerge. The full scope of the program will likely exceed available resources. In this context, it is anticipated that selections of particular projects within the scope of the issues will be determined by scientific peer reviews and programmatic relevancy reviews. Peer review will be help ensure the high quality of projects selected, which is of critical importance to both the regulatory application of the resulting information and the overall credibility of the Agency. Additionally, EPA will coordinate its efforts with other interested parties. After peer review of this research plan, EPA will prepare more laboratory-specific implementation plans for selected areas of research, and this plan will guide the development of solicitations under EPA's extramural grants program.

Figure 1. Risk assessment/risk characterization:
relationship of exposure assessment and effects assessment



Adapted from: Sexton *et al.* (1992)

Figure 2. Arsenic Research Strategy to Support Regulation Development



Key: PQL= practical quantiation limit
RSC = relative source contribution
RA = risk assessment
BAT = best available technology

CHAPTER I
ARSENIC RISK ASSESSMENT/CHARACTERIZATION

I.1 Background

The purpose of this Risk Assessment/Characterization Chapter is three fold. The first is to provide a description of the current risk assessments for ingested inorganic arsenic, thus clarifying the scientific basis for the regulations that have been developed from these risk estimates. The discussion also describes the strengths, uncertainties and identifies data gaps surrounding these assessments. Secondly, this chapter briefly outlines research opportunities that can improve the scientific basis for refining the current risk estimate. The research projects to address data gaps are discussed in the subsequent chapters on Exposure, Health Effects and Risk Management Research. Thirdly, this chapter discusses the ongoing and future risk assessment research, models and assessments that should be developed in order to fully characterize the risks associated with ingestion of arsenic and support refinement of existing regulations.

In this research plan, this risk assessment chapter serves as the focal point for identifying key data gaps and uncertainties in the current risk assessments and as the primary foundation for the research needed to fill those data gaps and reduce risk associated with ingestion of arsenic in drinking water.

I. 2 Characterization of arsenic risks: state of the science

This section reviews the risk assessment foundations of the current regulatory standards for arsenic in water and discusses the strengths and uncertainties in the interpretation of our current knowledge about arsenic exposures, health effects, and risks. The over-arching risk assessment issue addressed in this strategy is: determination of the risk associated with levels of arsenic to which people in the U.S. are exposed in drinking water. The evaluation of these risks includes consideration of the following issues, which are discussed below:

- Data on levels of human exposure to arsenic through drinking water and other major pathways;
- exposure levels at which such effects are observed and the closeness of those levels to levels found in U.S. drinking water;
- regulatory levels for arsenic in drinking water and ambient water ;

- an understanding of the variety of cancer and non-cancer effects induced by arsenic;
- supporting biological and mechanistic data that may aid in understanding arsenic risks; and
- quantitative risk estimates and their strengths and uncertainties.

This section discusses the current exposure and health risk assessments that have been developed to support existing regulations and guidance under the SDWA and CWA, CERCLA and RCRA.

Current Exposure Data:

(1) Arsenic in drinking water.

Currently, water utilities are only required to report arsenic concentrations that exceed to MCL of 50 µg/l. To develop a national picture of arsenic exposures from public drinking water supplies, data have been derived from four national surveys: 1) Community Water Supply Survey, 2) Rural Water Survey, 3) National Organics Monitoring Survey and 4) National Inorganics and Radionuclides Survey (U.S. EPA, 1983,1989, 1988). Detection limits ranged from 2-5 µg/l. Arsenic was detected in both groundwater and surface waters. Concentrations ranged from 0-100 µg/l. However, there is analytical uncertainty associated with the measurements and the analytical detection limits. In less comprehensive surveys, results were more variable; concentrations ranging up to 393 µg/l in Hidden Valley California (U.S.EPA 1980) have been reported. EPA has estimated that about 2% of the U.S. population is exposed to arsenic drinking water concentrations exceeding 10 µg/l, about 5% is exposed to concentrations above 5 µg/l, and about 15% is exposed to concentrations above 2 µg/l (Davis *et al.*, 1994).

(2) Dietary arsenic exposures

Dietary exposures are also of concern, since diet may contribute significantly to arsenic exposure. Since 1961, the U.S. FDA has systematically collected and analyzed food for arsenic as part of the Total Diet Study, also known as the Market Basket Study. Most recent data sets include food analyses conducted from April 1982 to April 1988 and June 1988 to April 1990 (FDA, 1992). A total of 234 foods were analyzed for arsenic content: foods were classified into one of 11 separate categories and total dietary intake averaged for three age groups (infant , toddler and adult). Using average daily consumption rates for each food group, total arsenic intakes of 21.5,

27.6. and 52.6 µg/day were estimated for infants, toddlers and adults respectively. These data address total arsenic content of foods. Because some common organic forms of arsenic are thought not to present toxicity concerns, this data should not be directly compared with drinking water intake information. Using some limited data on inorganic arsenic in foods (which can be more directly compared with water intake), Borum and Abernathy (1994) estimated that inorganic arsenic comprises about 20-25% of total dietary intake.

Current Health Risk Estimates:

Arsenic has been recognized as a potent human toxicant since ancient times and reports of human cancers associated with ingestion date to the last century. In recent decades, arsenic has been found to be carcinogenic by both ingestion and inhalation routes in multiple epidemiological studies (U.S. EPA, 1980, 1984, 1993, Tseng, 1968, 1977). Indeed arsenic is the only known human carcinogen for which there is adequate evidence of carcinogenic risk by both inhalation and ingestion. Arsenic is also the only carcinogen where exposure through drinking water has been clearly demonstrated to cause human cancer. Thus U.S.EPA has classified arsenic as a Group A carcinogen, i.e., a known human carcinogen, based on its 1986 guidance. This designation is used when there is sufficient evidence, generally from epidemiologic studies, to support a causal association between exposure to an agent and cancer. Problems with arsenic contamination in drinking water exist worldwide. Most recently arsenic exposures and health effects have been noted in a population of millions in India where arsenical ground waters have been substituted for surface water supplies.

EPA's cancer risk and RfD assessments for arsenic which are discussed below have been peer reviewed, adopted by the Agency, and appear as Agency consensus opinions on IRIS (U.S.EPA 1996).

(1) Foundations of the current arsenic regulations in water

As discussed previously, the regulatory and guidance levels under the SDWA and CWA vary widely. In 1975, EPA adopted 50 µg/l as a maximum contaminant level (MCL) for arsenic in drinking water under the SDWA. This level was developed by the Public Health Service in 1942 based on the acute or short-term toxicity associated with consuming high levels of arsenic. The arsenic MCL is not supported by a health-based risk assessment, rather it was adopted from

the U.S.PHS standard with the consideration of water intake of arsenic relative to total intake of arsenic from food. Using the information that was available then (dietary arsenic was estimated to average 900 µg/day) a consumption of 2 liters/day of drinking water containing 50 µg/l was estimated to contribute ~10% of the total ingested arsenic (U.S. EPA, 1975). Controlling water intake to less than 10% of the total intake was considered public health protective. As discussed above, more recent FDA data indicate much lower dietary arsenic intake than was assumed in this calculation.

More recently, a water quality criterion (WQC) of 0.018 µg/l for arsenic was established to protect humans consuming arsenic-contaminated water and 6.5 g of fish and shellfish/day under the CWA (U.S. EPA, 1980a, 1989, 1992). The WQC was calculated based on the recommendations and findings from U.S.EPA Risk Assessment Forum Technical Panel (1988) and the Ambient Water Quality Criteria Methodology (U.S. EPA, 1980b). It represents an intake associated with an upper bound incremental cancer risk of one-in-a-million. The WQC reflects the dose-response data for skin cancer from the Taiwan study (Tseng, 1968, 1977), use of age-specific prevalence rates for dose and a linear-quadratic dose response model to estimate lifetime risk of cancer. The use of a one-in-a-million risk level represents an EPA policy decision.

The EPA Risk Assessment Forum report upon which the standard was based was prepared by a Technical Panel convened in 1986. The purpose of the panel was to address issues relating to the qualitative and quantitative carcinogenic risk assessment for ingested arsenic. In particular, the panel examined issues relating to the validity of the Taiwan study and its application to U.S. populations, use of arsenic-induced skin lesions and the role of arsenic in human nutritional status (i.e., essentiality). The panel also evaluated information on genotoxicity, metabolism, body burden, tissue distribution, and the possibility for a cancer threshold. With regard to the Taiwan data, the panel evaluated validity of the study and applicability of the dose response assessment to the U.S. population, the interpretation and use of arsenic-associated skin lesions, and the role of arsenic in human nutrition. The panel concluded that: 1) the epidemiologic studies demonstrated that arsenic was a human carcinogen by the oral route; 2) the Taiwan studies provided a reasonable basis for quantifying the risks of skin cancers associated with the ingestion of inorganic arsenic in U.S. population; 3) an estimated unit risk range for water is $3\text{-}7 \times 10^{-5}$/µg/l; 4) the slope of the dose-response curve at doses below the range of observation may be less than linear, therefore the

calculated unit risk could overestimate the true risks[1]; and 5) arsenic may be a possible but not proven nutritional requirement in humans. Based on the peer-reviewed findings of this panel, the Risk Assessment Council recommended and EPA adopted the group A classification for ingested inorganic arsenic with a potency estimate of 0.0015/µg/kg/day and a unit risk for water of $5x10^{-5}$/µg/l.

(2) Weight of evidence discussion of the cancer data.

As noted above, EPA has identified arsenic as a group A "known" human carcinogen. Other organizations such as the International Agency for Research on Cancer (IARC) have also classified arsenic as a human carcinogen (U.S.EPA 1993). This classification is based on sufficient evidence of carcinogenicity from human data involving occupational and drinking water exposures. The Tseng *et al.* (1968) epidemiological study in Taiwan has played a central role in the current cancer assessment (and in the IARC cancer classification) and warrants special attention here. The Tseng *et al.* (1968) Taiwan study evaluated a large population (over 40,000) in comparison to other studies. Each participant was evaluated by a physician to identify skin lesions. Pathology was conducted on tissues collected from affected individuals. Older individuals were determined to have had long term exposure and there was a large control population for comparison. The population studied was characterized by age and covered a full range. Drinking water arsenic levels in the population studied by Tseng *et al.* (1968) were classified into three concentration strata (0-290 µg/l, 300-600 µg/l, and 600 µg/l over) and showed a clear dose response relationship with elevated skin tumor prevalence rates in all three strata. Skin tumor prevalence rates were elevated in both males and females, with the males showing a larger increase. With regard to the U.S. regulatory concern with drinking water the Tseng *et al.* (1968) data provide direct data on arsenic risks from the particular exposure media of concern and provide data on risks for levels much closer to those of regulatory concern than is the usual situation for environmental risk assessment. In the Risk Forum report, an estimation of skin cancer in a Mexican population exposed to arsenic was consistent with the results observed in the Taiwan study and supported the credibility of the risk estimates based on the Taiwanese data (Cebrian *et al.*, 1983).

[1]Additionally, it should be noted that a best estimate (MLE) rather than upper bound linear quadratic model was fit to the Taiwan data, thus there was also potential for underestimation of the true low dose slope.

As can be anticipated with a large and complex epidemiological study, a number of specific issues have arisen concerning the evaluation and interpretation of the Tseng *et al.* (1968) study. Several of these issues are worthy of note for the risk characterization:

Water concentration estimates in the Tseng study were made at the village rather than individual level. While grouped measurements are commonly employed in epidemiological studies (for example, use of area concentration rather than personal measurements in many occupational studies), this approach leads to uncertainties in the risk assessment. As concentrations in individual wells varied within villages, person-specific concentration data, were it available, might have allowed increased resolution of dose response patterns. Similarly, well concentrations exhibited temporal variability, and a larger number of measurements per well, using an improved analytical method, would have increased the precision of exposure estimates.

The potential for concomitant exposures to other contaminants in the Taiwan drinking water has also received attention. The arsenical water in Taiwan also contained humic substances. It has been speculated that these substances may be carcinogenic. However, humic substances are found in water supplies in many areas of Taiwan without observed elevations of cancer rates and the data for Taiwan show that cancer prevalence was correlated with arsenic concentrations in well water.

In a nutritional study, Yang and Blackwell (1961) suggested that the Taiwanese diet in the endemic Blackfoot area was deficient in methionine and fat. However, a recent reexamination of this data by Engel and Recevuer (1993) reported that the Taiwanese intakes for protein and methionine were within the now current recommended levels. It has been suggested that individuals with low intake of methionine may be less able to methylate arsenic and are potentially at higher risks of cancer.[2] The inverse correlation of cancer with dietary fat is contrary to current theory , as diets low in animal fat are widely recommended as a preventative measure to reduce cancer risks. This suggests that the risks observed in the Taiwanese population (including internal cancer mortality reported in later studies) might have been higher if they consumed a more typically western diet. There also exists uncertainty regarding the contribution of arsenic in food to total arsenic intake for individuals in the arsenic endemic areas.

[2]Hsueh *et al.* (1995) also found for individuals in the arsenic endemic area an association with high consumption of sweet potato with chronic carriers of hepatitis B surface antigen liver disfunction and an increase risk of skin cancer. The relevance of these findings for arsenic risk assessment is not clear.

The U.S. and Taiwanese populations differ in genetic characteristics, diet, and exposures to other environmental chemicals. Therefore, there is some uncertainty in the quantitative extrapolation of arsenic risks from one population to the other. However, for perspective, these uncertainties need to be compared with the greater degree of uncertainty involved when experimental animal results are applied to estimate human risks.

At the time of the 1988 Risk Forum report, the available data addressed primarily skin tumors resulting from the ingestion of arsenic. While some data on the relationship between arsenic and internal cancers was available in 1988, that data had not been fully assimilated into Agency risk assessment or management discussions. The fact that skin cancers are usually nonfatal led to Agency discussions of whether cancer risk estimates for arsenic should be "down weighted". However, further data on arsenic carcinogenesis at internal organ sites has become available in the intervening years.

More recent studies in the same area of Taiwan have reported a strong association between arsenic ingestion and increased mortality and incidence of internal cancers including cancers of the liver, bladder, kidney, and lung (Chen *et al.*, 1986). A recent study in Argentina (Hopenhayn-Rich *et al.*, 1996) has provided strong evidence that arsenic exposures in drinking water are associated with bladder cancer in a population that is very different from that studied in Taiwan. The contrast between the Argentine and Taiwanese studies in terms of ethnic background, dietary patterns, and potential for other constituents to be present in drinking water also serves in resolving concerns that some special characteristics of the Taiwan population or environment might have been responsible for the findings in the Tseng *et al.* (1968) study. Specifically, Hopenhayn-Rich *et al.* (1996) observed elevated rates of bladder cancer in an arsenic exposed population that consumed large amounts of animal protein and where humic substances were not identified in the water. Studies in England (Cuzik *et al.*, 1992) and Japan (Tsuda *et al.*, 1990)also contribute to the weight of evidence that ingested arsenic causes bladder cancer. Studies conducted in the U.S. have not demonstrated an association between arsenic in drinking water and skin or internal cancers. While there was no demonstrated elevated cancer incidence in some limited U.S. populations, the population sizes were too small and/or exposure times too short to expect to see an effect.

(3) Non-cancer assessment:

In addition to the cancer effects observed in epidemiologic studies, arsenic exposures have also been reported to result in adverse non cancer health effects in humans. These effects include hyper-pigmentation and hyperkeratosis and cardiovascular effects. A risk assessment for non-cancer effects associated with exposures to inorganic arsenic was also developed using data for the Taiwanese population previously studied for skin cancers (Tseng, 1977) and considering the drinking water and potential dietary arsenic intake in the study. An oral RfD of 0.3 µg/kg for inorganic arsenic was developed based on the absence of hyper-pigmentation, keratosis or documented vascular complications in the study control group (U.S. EPA, 1996b). The RfD for was based on a NOAEL of 0.8ug/kg-day which included intakes of 9ug/l of arsenic in water and 2ug/day in food. The RfD was calculated using the NOAEL of 0.8ug/kg-day and applying an uncertainty factor of 3. It was verified by the Agency's RfD/RfC Workgroup on 11/15/90 and given a medium confidence. Members of the RfD workgroup identified a range of values as candidates for the RfD, depending on the particular assumptions made about arsenic exposures in the study group where adverse effects were not observed and with different potential choices of a data base uncertainty factor. There was not a consensus among workgroup scientists on a single value for an oral reference dose. The EPA Risk Assessment Council selected a RfD of 0.3 µg/kg/d for total inorganic intake and concluded that strong scientific arguments could be made for various values within a factor of 2 or 3 of the recommended RfD value, i.e., 0.1 to 0.8 µg/kg/d. If exposures were solely from water, this would amount to 21 µg/day for adults (or 10.5 µg/l, assuming consumption of 2 l/day). The discussion on dietary exposures above in Section 1.2 suggests that background exposures are already 50-100% of that value.

(4) Metabolic and mechanistic data -- current contribution to risk assessment

In recent years research has provided significant information about the biological effects of arsenic including its genotoxicity (chromosomal and DNA changes) and metabolism. The "state of the science" of our current understanding of arsenic mechanisms is addressed in some detail in chapter 3. However, our understanding of the mechanism of action of arsenic carcinogenesis (and other toxicity) is very limited in its ability to support meaningful biological conclusions about the shape of dose response relationship below the range of observed effects. EPA is planning an expert workshop for early in 1997 to discuss mechanisms of action; the recommendations from this workshop are expected to help shape future research directions.

Some scientists, including a panel of the EPA SAB, have focused on evidence for dose dependent methylation as potentially supporting changes in the dose response modeling for arsenic or suggesting that "apparent thresholds" exist. Currently, our understanding of the role that methylation plays in the induction of toxicity is limited; methylation may either reduce or potentiate toxicity. Data indicate that substantial quantities of both inorganic and methylated arsenic are excreted in urine at both high and low exposure levels. Thus it now seems unlikely the data on arsenic methylation would support major changes to conclusions about anticipated arsenic risks at low doses.

Further research into the mechanisms of arsenic toxicity may make important contributions to arsenic risk assessment, as suggested by EPA's recently proposed cancer risk assessment guidelines. Research opportunities are discussed below. However, the current U.S. standard for drinking water is within an order of magnitude of concentrations at which cancers and other health effects have been seen in epidemiological studies. The closeness of arsenic "effect levels" and levels of regulatory concern limits the potential impacts of refinements to the arsenic risk assessment for practical decision making needs. To have a practical impact, our expectations about arsenic risks would have to be markedly changed (reduced) within a narrow dose window just below the range of epidemiological data. Even if strong nonlinear effects were to be identified in fundamental biological processes, two factors would limit the impact of this information. The expected diversity of human responses to arsenic and the substantial "background" dietary exposures to arsenic would suggest that mechanistic findings may not be likely to support sharp changes to the arsenic risk picture within the range of current regulatory concern.

I.3 What are the research opportunities to improve/refine current risk assessments?

This section identifies and briefly discusses the research opportunities associated with improving the existing risk and exposure assessments. The information is organized by key research questions that relate to the uncertainties in the risk and exposure assessments previously described. This section highlights key research opportunities in order to set the direction for the research that is discussed in the following chapters on Exposure, Health Effects and Risk Management Research.

Exposure Assessment:

Most available data on arsenic address total arsenic concentrations and do not distinguish between arsenic valence states or inorganic versus organic forms of arsenic (U.S. FDA, 1978,1988, 1990). In a number of the research efforts discussed in this plan it is important to distinguish between different chemical forms of arsenic, that is to "speciate" arsenic during chemical analysis. The importance of data on the chemical form of arsenic depends on the environmental media being addressed and the intended application of the data. Arsenic present in water is primarily in the form of inorganic arsenic (III and V); arsenic (III) is oxidized during water treatment to arsenic V. In this research strategy, distinguishing between the inorganic forms of arsenic in water is not considered to be important for assessing arsenic risks. However, a particular concern is the need to distinguish between inorganic and organic forms arsenic in assessment of dietary exposure. To be comparable with data on drinking water (which contains inorganic arsenic), dietary assessments need to measure levels of inorganic arsenic present in foods, and differentiate it from organic arsenic. Food and water are thought to be the main contributors to arsenic exposures; dermal exposures from soil and water, and inhalation exposures, are believed to be very minor contributors to arsenic exposure (ATSDR, 1993; Borum and Abernathy, 1994).

More recently, secondary concern has been raised regarding some specific forms of organic arsenic (i.e., mono- and di-methyl forms) found in some foods (ATSDR 1993) and for which toxicity issues may exist. Pharmacokinetic research also requires data to distinguish between the organic and inorganic forms of arsenic found in biological samples. The strategy for exposure assessment research includes work to improve methods for the reliable speciation of arsenic. A primary challenge of this research is the reliable extraction of arsenic compounds from complex dietary and biological samples in order to adequately asses intake and tissue levels.

Research Opportunities:

- Arsenic speciation: Improvements in analytical methods for arsenic particularly for diet and biological materials. A primary concern is distinguishing between inorganic and organic arsenic, with specific organic forms of arsenic also warranting attention.
- Measurement of background exposures to arsenic in U.S. population, particularly addressing inorganic arsenic intake in the U.S. diet. This research should address both the cumulative intake of arsenic and its bioavailability.

- Development and evaluation of biomarkers of exposures that may aid in the assessment of levels of human exposures and contribute to the assessment of arsenic bioavailability.

Cancer Assessments:

Although epidemiologic studies have clearly shown a causal relationship for increased cancer risks in individuals having exposures to arsenic in drinking water, there are a number of areas where further empirical data could broaden and strengthen our ability to assess arsenic risks.

Research Opportunities:

- Further development of data on the several types of internal cancers that have been associated with arsenic exposures.
- Dose response data on hyperkeratosis as a likely precursor to skin cancer, which, due to a higher rate of incidence among arsenic exposed individuals, can be studied at lower exposure levels.
- Research on factors influencing human susceptibility including age, genetic characteristics and dietary patterns.
- Metabolic and pharmacokinetic studies that can identify the presence of dose dependent metabolism and aid in the evaluation of mechanistic data.
- Mechanistic studies for arsenic-induced genotoxicity and carcinogenicity (for example, induction of genetic damage and tumor promotion in some experimental systems). Mechanistic data, if reliably linked to human carcinogenesis by arsenic, may provide insight into susceptibility and dose response.

Noncancer Assessments:

Several epidemiologic studies have observed that arsenic exposures result in adverse effects other than cancer. Clear associations were observed for hyperkeratosis, hyper-pigmentation and peripheral vascular effects, and a study with a U.S. population reported neurological effects. Other effects such as gastrointestinal and liver effects and diabetes have not been clearly defined. Additional studies can better define the potential risks associated with these health effects. In addition, studies can address the influence of other elements on arsenic toxicity.

Research Opportunities:

- Development of human dose-response data for hyperkeratosis, cardiovascular disease,

neurotoxicity and developmental effects.

- Development of additional health effects and hazard identification data on other non cancer endpoints such as diabetes and hematologic effects.

Risk Management Research

Further development of treatment options for the removal of arsenic from drinking water will contribute to informed decision making and can support the development of regulatory standards that are protective of public health. Uncertainty exists as to effectiveness and costs of control technologies for removal of arsenic to levels being considered. Of particular concern is the development of cost effective treatment options for small systems.

Research Opportunities:

- Identification of limitations of treatment technologies and impacts on water quality
- Development of treatment technologies for small water systems.
- Development of data on cost and performance capabilities of various treatment options.
- Consideration of residuals management issues, including disposal options and costs.

I.4 Risk Characterization Research: Health and Exposure Assessment

As noted above, there are several strengths, issues and uncertainties associated with the arsenic database and current risk assessments. In particular, issues exists with the interpretation of human studies, linearity of the dose response at doses below the range of observed effects, toxicity of specific arsenic species and extrapolation of dose to arsenic exposures in food and water of U.S. populations. Concern also exists regarding the level of protection associated with the drinking water MCL of 50 µg/l which was developed from presumed high exposure to "total" arsenic in the 1940s.

This section discusses the research issues and activities that address improving the current health and exposures assessments and risk estimates. In addition, it describes research projects in the areas of risk assessment methods and model development that are either ongoing or needed to address data gaps in developing or refining current risk assessments for arsenic (i.e., risk estimates). It also identifies projects that are needed to better characterize the risk associated with exposures to arsenic (i.e., integration of health and exposure data).

This section and the following section will only cover risk assessment research, since more discussion of exposure, health effects, and risk management research will be addressed in Chapters 2, 3 and 4, respectively.

Risk Assessment/Characterization:

The risk assessment/ characterization consists of a comprehensive evaluation and integration of the health effects (cancer and non-cancer) induced by arsenic; the evaluation of dose response data including the development of quantitative risk estimates, and the identification of strengths and uncertainties. This process considers both direct data on arsenic toxicity as well as supporting biological and mechanistic data. The preceding discussion has highlighted a number of issues and research questions that can be addressed to better refine and strengthen risk estimates. Risk assessment tools and methods should address the integration of newer scientific information and data for risk assessment and risk characterization. Agency risk characterization guidance stresses the need for analyses to address central and high end estimates of individual risk as well as population risks. Better characterization of exposures including identification of high risk populations will contribute to informed decision making for arsenic risks.

In addition, EPA has established guidance or regulations for arsenic under the Clean Water Act (CWA) and Safe Drinking Water Act (SDWA). As discussed previously these values vary widely which has resulted in much confusion and difficulty in implementing State and Local programs. The 1996 amendments to SDWA require the Agency to re-assess and revise current MCLG and MCL by 2001. EPA is also faced with the dilemma of providing guidance to State and local communities on the health risk associated with exposures to arsenic from drinking water while the regulation is in a stage of transition.

Refinement of the quantitative risk assessment is intended to provide a clarification of the dose response and biological relationship for arsenic induced skin cancers and the development of risk assessment tools for interpreting the dose response relationship in humans. Data exist on internal cancers from several published studies, in addition a number of epidemiologic studies have been initiated to further investigate the risks for internal cancers. Additional work on dose response assessment for internal cancers is needed. This assessment would aid in defining the magnitude of risks from internal cancers and serve as the basis for comparison to skin cancer risks.

In addition to dose response assessments, comprehensive exposure assessments are required to evaluate the relative magnitude of population exposed to arsenic from diet and water. Previous dietary estimates assumed balanced diet and average nutritional status and do not take into account ethnic, cultural or economic impacts on food consumption patterns. Improved exposure assessment of background rates will allow for the better risk characterization and comparative risks.

Research Opportunities to Strengthen Risk Assessment:

- Development of risk characterizations to provide interim support to States and local communities on health risks associated with the exposures to arsenic contaminated drinking water.
- Comprehensive assessment and analysis of existing data on risks of internal cancers, including consideration of quantitative dose response models.
- Development of predictive tools and statistical models for assessing bioavailability, interactions and dose-response as better mass balance data become available.
- Comprehensive assessment of exposure levels and incorporation of data into risk estimates for better characterization of actual risks associated with arsenic exposure.
- Comprehensive assessment of arsenic mode of action provide a greater understanding of biological mechanisms and factors that may impact the shape of dose response curve. Consideration of implications of these factors for risk assessment in human populations.
- Comprehensive assessment of non-cancer risks and consideration of appropriate modeling tools for quantitative estimation of non-cancer risks.
- Assessment of existing information on arsenic interactions with other metals to predict if response is additive or departures (i.e. synergism, antagonism) from additivity can be estimated.

Ongoing Activities

EPA is in the process of re-evaluating the risk assessments for arsenic as part of IRIS Pilot Program. This re-evaluation will cover both cancer and noncancer risks and will to the extent available include data not previously reviewed as well as application of proposed revisions to the Agency's Cancer Risk Guidelines. As part of this reassessment, the Agency is conducting a Workshop on biological mechanisms for arsenic induced carcinogenicity and implications for extrapolating below observed dose response range.

I.5 Proposed Risk Assessment Research and Risk Assessments

Risk Assessment Issue 1. Development of Risk Assessment Tools/Models

1a. Development of Statistical Models for Analyzing and Modifying the Dose-Response Curve

The dose-response estimate for arsenic was developed based on human data from the Taiwan study. Low dose risk estimates were developed by applying age specific prevalence rates for dose and a linear-quadratic dose response model to estimate lifetime risk of cancer. The goal of this effort would be to develop appropriate risk assessment models for refining the current low dose estimates used in the current risk assessments. These models would be developed after appropriate data on metabolic rates and tissue dosimetry generated in human or animal studies described in the Health Effects chapter have been completed. Although the need for developing these models is important, it is dependent on the development of biological data and must be sequenced in with the conduct of these studies.
Medium priority; intramural

1b. Development of Predictive Risk Assessment Models and Tools for Assessing Arsenic Interactions and Mode of Action.

There are several studies suggesting a strong interrelationship between arsenic and various trace minerals and essential elements. These studies indicate that arsenic interacts with these elements both environmentally and biologically. Interactions with selenium and zinc have shown a reduction in arsenic-induced toxicity, while interactions with lead and cadmium may increase toxicity. The goal of these studies would be to develop predictive models and risk assessment tools to assess the potential interactions of arsenic with other elements in drinking water. Models would elucidate the mechanism i.e. additivity of arsenic toxicity for noncancer toxic effects based on the possible interactions. Information can contribute to biologically-based risk assessment by taking into account interactions of arsenic with trace minerals and essential elements.
Medium priority; intramural and extramural

1c. Development of dose response models for internal cancers

In addition to skin cancers, several studies have been published that indicate arsenic exposures may induce internal cancers. A number of studies have been initiated to further investigate the relationship of arsenic exposures with increased incidence of internal cancers. Statistical analysis and development of dose response models are needed to apply data from these studies to determining risks of internal cancers.
High priority; intramural and extramural

Risk Assessment Issue 2. Development of Risk Assessments/Guidance and Risk Characterizations for Arsenic

2a. Workshop on Mode of Action for Arsenic.

The workshop will examine and assess current information on the mechanisms by which arsenic induces carcinogenicity. This workshop, an ongoing joint effort of OW and ORD, will focus on the mode of action of arsenic which, given adequate mechanistic data could provide insights on the shape of the dose-response curve below the observed range. The workshop will also address factors to be considered in assessing potential departures from linearity and impacts on risk assessment. In addition, results can contribute to further definition of research needs in the area of mechanistic studies.
High priority; intramural and extramural.

2b. Development of Interim Guidance for Use By States and Regions in Setting Water Standards

Based on information currently available data and assessments (including the IRIS summary and the mechanisms workshop report), ORD will work with OW to develop interim guidance to assist Regions, States and local communities in dealing with arsenic-contaminated drinking water and permitting issues. The focus of this effort will be to develop risk estimates or other qualitative guidance for arsenic concentrations in the 2-50 µg/l range of regulatory interest.
High priority; intramural and extramural

2c. Assessment of Exposure Data

This effort will focus on the development of a preliminary risk assessment of existing exposure data to investigate background exposures and speciation, and their correlation of intake/blood/urine levels. This information will also be integrated with hazard and dose information to estimate toxicity at low doses. The goal is to provide a range of risk estimates for various exposed populations, develop correlations for adult and child levels and media, i.e., diet and water. Data from an ongoing EPA cooperative study with Harvard will be analyzed, as well as data from exposure databases such as NHEXAS amd NHANES 3. A risk characterization summary will be developed for use in generating Regional, State and local community interim guidance.

High priority; intramural and extramural.

TABLE I-1. RISK ASSESSMENT RESEARCH STRATEGY MATRIX FOR ARSENIC

ISSUE	TASK	PRODUCT	USE*
RA. Issue 1. Development of risk assessment tools/models	RA Task 1a. Development of statistical models for analyzing and modifying the dose-response curve. Medium Priority	Refinement of risk estimate for arsenic, revised IRIS summary	Development of MCL - OW, States and local communities, ORD, OSWER
	RA Task 1b. Development of predictive models for assessing interactions. Medium Priority	Improved risk characterization of arsenic assessment, revised IRIS summary	Support for MCL- OW, OSWER, DOE
	RA Task 1c. Development of dose response models for internal cancers. High Priority	Determination of the risks of arsenic induced internal cancers	Development of MCL - OW, States and local communities, ORD, OSWER
RA. Issue 2. Development of risk assessments/guidance and risk characterization for arsenic	RA Task 2a. Workshop on mode of action. High Priority	Summary report and revised IRIS File	Development of interim guidance for Regions, States and local communities
	RA Task 2b. Development of guidance for use by States and Regions. High Priority	Interim guidance and assessments	States and Regions, DOE development of regulations and permits.
	RA Task 2c. Assessment of exposure data. High Priority	Report characterizing human exposures	Exposure assessment and refinement of risk estimates OW, ORD, OSWER, DOE

*OW = Office of Water; ORD = Office of Research and Development; OSWER = Office of Solid Waste and Emergency Response; DOE = Department of Energy

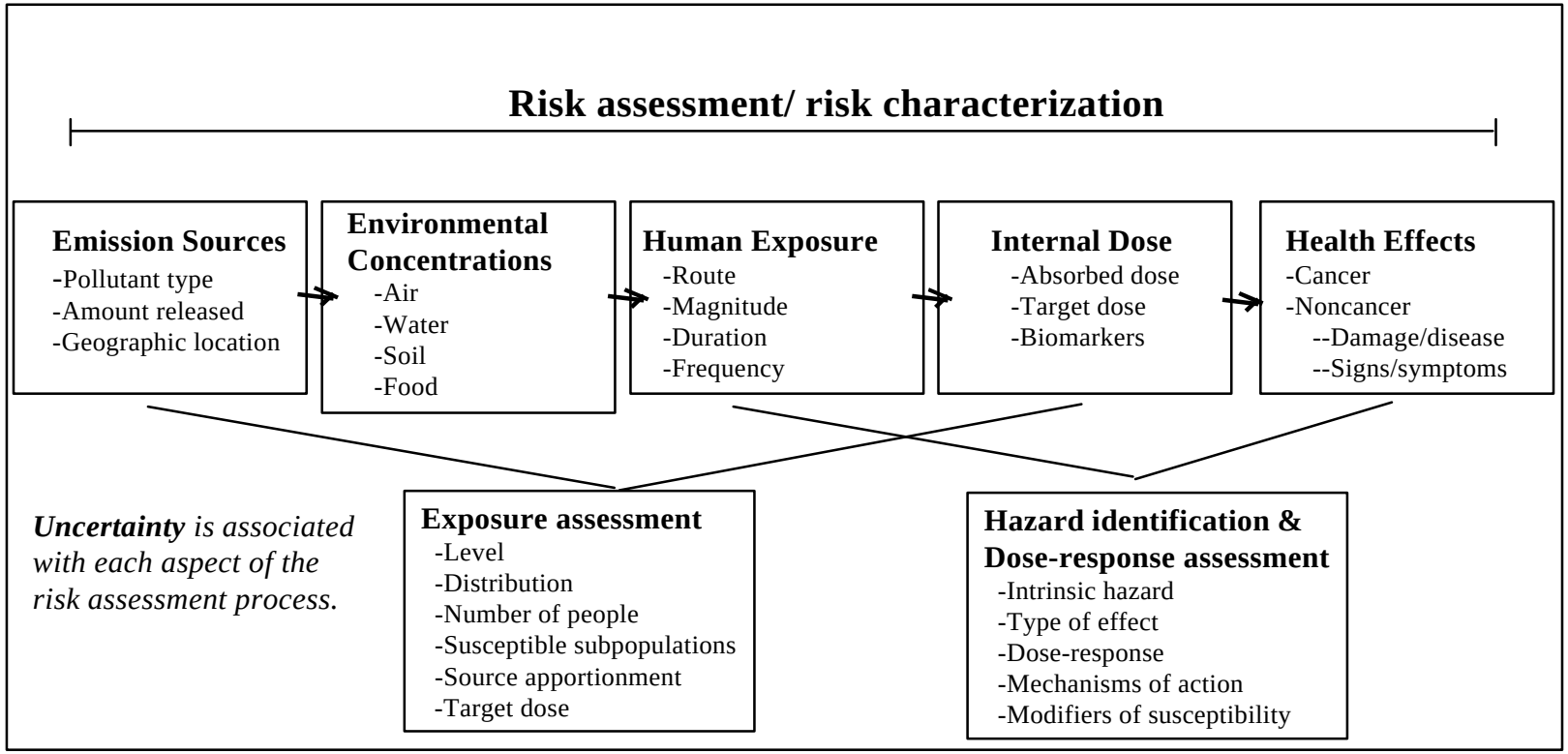
TABLE I-2. RISK ASSESSMENT TASK SUMMARY, CURRENT ACTIVITIES AND PROPOSED SEQUENCE FOR STUDIES

	TASK[1]		ON-GOING	Priority	TIME FRAME[2]					
Short Study Title	I	E	Y/N	Priority	FY97	FY98	FY99	FY00	FY01	FY02
RA Task 1a. Development of statistical models for analyzing and modifying the dose-response curve	I		N	Medium		EPA	EPA			
RA Task 1b. Development of predictive models for assessing interactions	I	E	N	Medium	EPA	EPA	EPA			
RA Task 1c. Development of dose response models for internal cancers	I	E	N	High		EPA	EPA			
RA Task 2a. Workshop on Mode of Action	I	E	Y	High	EPA					
RA Task 2b. Development of interim guidance for States and Regions	I	E	N	High	EPA	EPA				
RA Task 2c. Assessment of exposure data	I	E	Y	High	EPA	EPA				

[1]I=Intramural (EPA inhouse research), E=Extramural (EPA sponsorship through grant or coop)

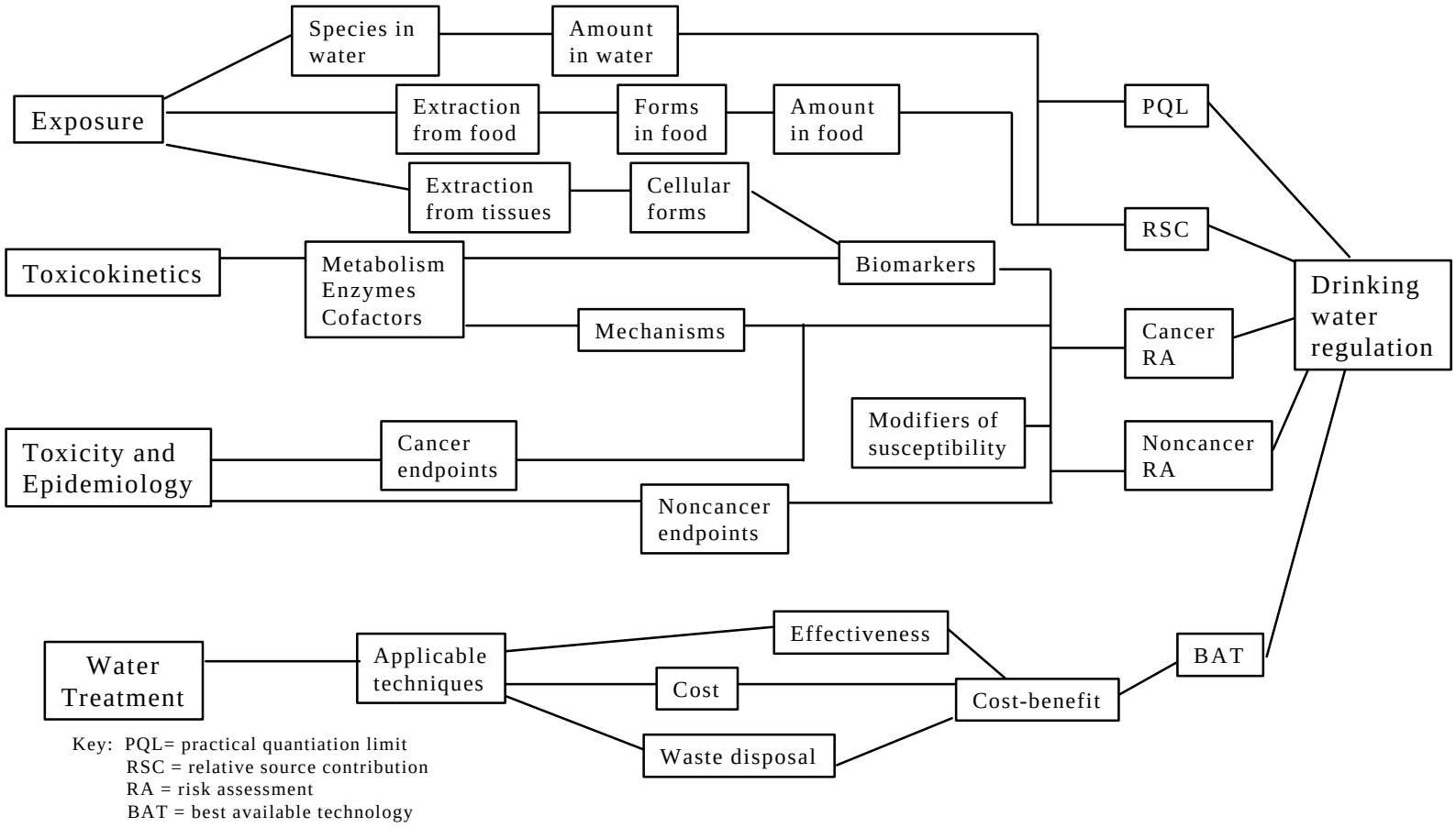
[2]EPA=EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort
X=EPA resources insufficient to address these tasks, need external effort

Figure 1. Risk assessment/risk characterization:
relationship of exposure assessment and effects assessment



Adapted from: Sexton *et al.* (1992)

Figure 2. Arsenic Research Strategy to Support Regulation Development



Key: PQL= practical quantiation limit
RSC = relative source contribution
RA = risk assessment
BAT = best available technology

CHAPTER II
EXPOSURE TO ARSENIC SPECIES: ANALYSIS METHODS AND HUMAN EXPOSURES

II.1 Background

Arsenic in surface and ground water originates from both geological and anthropogenic sources. The geographic distribution of arsenic in surface and ground waters in the U.S. has been estimated (Frey *et al.*, 1996). Based on a national survey of 140 utilities, representing 36% of the U.S. population, it has been projected that ~15% of the U.S. population is exposed to arsenic in drinking water at levels greater than 2 μg/l (ppb). These estimates drop to 5% and 2% for arsenic concentrations of 5 μg/l and 10 μg/l, respectively (Davis *et al.*, 1994). The reliability of this estimate at 2 μg/l is of some concern given the detection limits of the analytical methods used and the variability associated with analytical measurements near the detection limit. Much higher levels in drinking water (i.e., in excess of 80 μg/l) have been reported in isolated areas in the western United States. These elevated concentrations are commonly, but not exclusively, associated with ground waters (Frey *et al.*, 1996). Arsenic in drinking water is predominately inorganic and is comprised of arsenate (arsenic (V)) and arsenite (arsenic (III)). These inorganic species can interconvert depending on the oxidative or reductive nature of the water. The inorganic arsenic occurs in drinking water mainly in the form of arsenate, although arsenite has been reported in waters that are anaerobic or very low in dissolved oxygen (ATSDR, 1993). Air levels of arsenic in the United States[1] are generally quite low with a reported range of average site concentrations of 0.01 to 0.45 $\mu g/m^3$ (Borum and Abernathy, 1994).

Arsenic is extremely mobile in the aquatic environment. Naturally occurring and

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1 Data from the Aerometric Information Retrieval System (AIRS) air monitoring database of the EPA Office of Air Quality Planning and Standards (OAQPS) for the years 1980-91; based on a reporting limit of 0.01 μg/m3, arsenic was detected at 118 of 257 sampling sites.

of the arsenic. For instance, marine fish and shellfish are high in forms of arsenobetaine that are considered to be essentially nontoxic (ATSDR, 1993). Using a "total" arsenic content of foods to evaluate dietary exposure (µg/day) is not an accurate risk indicator because of the toxicity differences of the various arsenic species which are merely added together in a non-speciated arsenic exposure assessment. The arsenic species, in at least organic and inorganic fractions, need to be determined to adequately characterize risk.

Arsenic ingested in the form of arsenate is first non-enzymatically reduced to arsenite and then undergoes enzymatic methylation to MMA and DMA in the liver (Styblo *et. al.*, 1996). Methylated metabolites, arsenate and arsenite are primarily excreted in urine. The concentrations of these metabolites in urine are generally accepted as the most reliable and toxicologically relevant indicator of recent or on-going arsenic exposure. Arsenic in hair and fingernails is considered a better indicator of past exposure. Blood concentrations of arsenic species are also relevant indicators of recent arsenic exposure and are less susceptible to contamination during collection and provide greater likelihood of maintaining the arsenicals in their ingested forms.

Issues in quantifying environmental exposure contributes to uncertainties in the exposure-dose-response chain in human epidemiologic studies and arsenic risk assessment. This is an important issue because it impacts dose–response assessment, which impacts quantitative risk estimation. This chapter describes key exposure-related issues and anticipated research designed to address arsenic exposure risk assessment needs. These research issues include estimating species-specific arsenic exposure from environmental media (water, soils, diet) and estimating the bioavailability of arsenic species from various media including biomarkers of exposure.

II.2 What Analytical Methods Are Needed For Determining Arsenic In Exposure Assessment Media?

State of the Science

[Note: The word <u>total</u> could be a point of confusion in the following sections because <u>total</u> in an exposure study often refers to the consideration of all possible exposure routes. In an analysis context, as used below, the word "total" refers to chemical analysis of the total arsenic content in a sample. Speciation is another word which can lead to confusion. Speciation is defined as the separation, identification, and quantification of the chemical forms of arsenic. This separation can be as simple as inorganic arsenic from organic arsenic or as complex as complete separation into

individual arsenicals. The appropriate degree of speciation is often dependent on the application.]

Analytical methodologies which are used for arsenic monitoring under the Safe Drinking Water Act, Clean Water Act, and Resource Conservation and Recovery Act all report "total" arsenic. "Total" arsenic is defined as the solubilized arsenic within the sample after a digestion with hot mineral acids (USEPA, 1971). The digestion oxidizes the matrix (soil, food, biological), solubilizing the available arsenic species without regard to the chemical form or oxidation state of the arsenic. These analytical methodologies, written by EPA (USEPA, 1994 and 1986), ASTM (ASTM, 1995) and SM (SM, 1995), NIOSH, and USGS, include guidance on sample preservation, laboratory sample handling, and sample digestion. Atomic spectroscopy is the foundation of these analytical methodologies for determining "total" arsenic in air, water, soils, foods, and biological fluids. For instance, "total" arsenic in the FDA's market basket of common foods is determined using an aggressive digestion followed by hydride generation coupled to an atomic absorption spectrometer. These methods provide detection limits as low as 100 ppt (ng/L) by direct analysis using an inductively coupled plasma mass spectrometer (ICP-MS).

Virtually all the data available for arsenic exposure assessment is based on "total" arsenic determination. "Total" arsenic concentration is a relatively poor indicator of the risk associated with an arsenic exposure because the chemical form of the arsenic strongly influences its toxicity (ATSDR, 1993). The "total" arsenic digestion used in EPA, USGS, NIOSH, FDA, ASTM, and SM, methodologies changes the chemical form of the arsenic resulting in a complete loss of species-based toxicity information. Therefore, certain aspects of characterization of arsenic exposure requires species-specific analytical methodologies capable of providing reliable individual arsenical concentrations.

Speciation-based arsenic analysis partitions the "total" arsenic into at least inorganic vs. organic prior to detection. The analytical difference between "total" and speciation-based methodologies is that the speciation-based methods preserve the chemical form and separate the individual arsenic species prior to detection. This analytical difference implies the need to ensure species-specific integrity from sampling to detection. In terms of instrumentation, an interface to chromatographic techniques (liquid chromatography (LC), ion chromatography (IC), capillary electrophoresis (CE)) is required. In this respect, a speciation-based method is analytically very different than a "total" arsenic determination. To date, these differences have **not** been adequately addressed in the form of arsenic speciation methodology by the EPA, FDA, USGS, NIOSH,

ASTM or SM. In speciation-based analysis, separation schemes (IC, HPLC, CE) have been interfaced to hydride atomic absorption (Gailer *et al.*, 1994, Hasegawa *et al.*, 1994, Lopez *et al.*, 1993, Haswell *et al.* 1985), inductively coupled plasma atomic emission spectrometer (ICP-AES) (Alberti *et al.*, 1995, Low *et al.*, 1986, Valez *et al.*, 1995) and inductively coupled plasma mass spectrometer (ICP-MS) (Beauchemin *et al.*, 1989, Hansen *et al.*, 1992, Thomas *et al.*, 1995, Story *et al.*, 1992, Hwang *et.al.* 1994, Branch *et al.*, 1994, Larsen *et al.*, 1993, Le *et al.* 1994, Magnuson , 1996a.) for the speciation of arsenic in a variety of matrices. These manuscripts demonstrate a particular aspect of an analytical approach or a unique capability in the area of arsenic speciation. They represent the state-of-the-art in chromatographic technology and innovative detection schemes, but they seldom address all the aspects necessary to formulate an analytical methodology. A complete methodology should address the following questions: 1.) What sampling protocol will assure species-specific integrity? 2.) How can the matrix be eliminated without the destruction of speciation-based information? 3.) What components of a matrix cause spectral and chromatographic interferences?

The peer reviewed literature contains references for the speciation of arsenic in 1) water (Hasegawa *et.al.*, 1994, Haswell *et.al.*, 1985, Hwang *et.al.*, 1994, Thomas *et.al.*, 1995, Magnuson *et.al.*, 1996a.), 2) biologicals (Arbinda *et.al.*, 1995, Heitkemper *et.al.*, 1989, Larsen *et.al.*, 1993, Low *et.al.*, 1986, Story *et.al.*, 1992), 3) and foods (Alberti *et.al.*, 1995, Beauchemin *et.al.* 1989, Branch *et.al.*, 1994, Larsen *et.al.*, 1993, Le *et.al.*, 1994, Lopez *et.al.*, 1993, Velez *et.al.*, 1995). While these manuscripts represent the technical framework for a method, considerable research will be required before these can be adopted as exposure assessment tools by the Agency. The major analytical challenge will be assuring that the arsenic species which are within the sample, are the same as those detected i.e., that the extraction, preparation, separation, and detection do not alter the distribution of arsenic species.

The following research issues provide some general direction and time frame for refinement of arsenic speciation methods which are needed in all aspects of arsenic research. The ideal approach would be to develop an extraction and sample preparation scheme that is compatible with a flexible and cost-effective separation and detection scheme. Finally, emphasis in developing a speciation method should be placed on demonstrating the procedure's capability of assuring species-specific integrity from sampling through detection. The integrity of the species is critical to toxicological and pharmacokinetic investigation.

Sample Preservation And Preparation: Many liquid samples can be analyzed with little preparation but the extraction of species-specific information from solid samples is a relatively new area (Alberti *et al.*,1995, Larsen *et al.*, 1993, Le *et al.*, 1994, Valez *et al.*, 1995). Therefore, solids (foods) and tissue-based matrices requiring speciation information are longer term projects (3-5 years) as opposed to the speciation of arsenic in water (Hwang *et al.*,1994, Hasegawa *et al.*, 1994, Haswell *et al.*, 1985, Thomas *et al.*, 1995, Magnuson *et al.*, 1996a) and urine (Larsen *et al.*, 1993, Low *et al.*, 1986, Story *et al.*, 1992) (1-3 years).

Separation Techniques: The separation system (LC, IC, CE) should provide relatively short analysis times, tolerate diverse matrices, such as drinking water and urine, and be compatible with sensitive but conventional detectors. Given the current state of the science in the separation of arsenicals, ion chromatography demonstrates a good balance of the above attributes (Arbina *et.al.*, 1996, Martin *et.al.*, 1995, Magnuson *et.al.*, 1996a). An ion chromatography separation for arsenite, arsenate, MMA and DMA has been demonstrated (Magnuson *et.al.*, 1996a) in the literature making its evaluation a short term project (1 year). On the other hand, capillary electrophoresis has shown some initial capability (Magnuson *et.al.*, 1996b), but this approach has sample injection and matrix limitations, which would require considerable research making it a long-range goal (3 years).

Detection: The cost-effectiveness of speciation will be driven by the capability of the separation scheme to be interfaced to existing instrumentation such as atomic absorption, inductively coupled plasma atomic emission spectrometer and inductively coupled plasma mass spectrometer. These detector interfaces are similar to those used in "total" arsenic methods making their adaptation easier and less research intensive. (Immediate -2 years) The applicability of atomic absorption and inductively coupled plasma atomic emission spectrometry to the detection of environmentally significant concentrations of arsenic species would be limited without the use of hydride generation to improve sensitivity. Hydride generation also affords some freedom in choosing a mobile phase for the chromatographic separation. The use of hydride generation will require an on-line digestion prior to detecting the highly derivatized arsenicals, i.e., arsenobetaine.

Ongoing EPA Research

The ongoing research in the area of arsenic speciation has focused on utilizing a membrane gas liquid separator with ICP-MS detection. This work has evaluated separation schemes

(LC and CE) for the speciation of arsenic in saline matrices. These saline matrices closely r the analytical difficulties associated with biological matrices, therefore, the initial use of salin matrices represent a logical analytical progression towards biologicals. This approach will pro a more sensitive method for monitoring purposes.

II.3 What Data Are Required To Adequately Assess Arsenic Exposure In Human Populations?

State of the Science

Arsenic exposure assessment requires evaluation of the relative contribution of both (1) *media* (water, food, etc.) and (2) *pathways* of exposure (oral, inhalation, dermal). For non-occupationally exposed individuals it is generally believed that uptake of arsenic via dermal exposures from soil and water, and inhalation are very minor contributors to total exposure; whereas intake from food and water accounts for nearly all environmental arsenic exposure (ATSDR, 1993; Borum and Abernathy, 1994). The major exception to this might be populations in the vicinity of arsenic emitting industrial facilities or areas where soils are contaminated with arsenic. Food is generally estimated to be the major contributor to "total" arsenic exposure. However, estimates for the contribution of drinking water to total human arsenic exposure vary between 63% and 22% depending on the assumptions used in the analysis, and could be up to 99% in some areas in the western United States where there is low consumption of fish and shellfish (Borum and Abernathy, 1994). For example, Native American and Alaska Native studies have indicated average seafood consumption rates up to ten times greater than the U.S. EPA average estimate of 6.5 gram/day (CRITFC, 1994; Wolfe and Walker, 1987; George and Bosworth, 1988; Nobmann, *et al.*, 1992; and Tulalip Tribe, 1996). For these populations, total arsenic derived from seafood and other foods may be important exposure sources in addition to drinking water. Such exposure assessments need to consider species-specific toxicity of the various arsenic forms to accurately reflect the risk.

In most epidemiologic studies used for quantitative risk estimation of ingested arsenic, only non-speciated arsenic intake data are available for drinking water and food. This may not be a serious limitation in situations where drinking water (predominately inorganic arsenic) can be verified to be the major source of arsenic exposure. The degree to which this is a limitation in the United States is difficult to determine because of the lack of a national occurrence database for arsenic in drinking water. However, the contribution of diet to human exposure of arsenic should

be considered a potentially important issue for any population since less than half of the water ingested is in the form of drinking water. Drinking water is also ingested as part of foods or beverages (i.e., coffee, tea, juices, etc). Where arsenic levels in public drinking water supplies are relatively low, the contribution of food to total arsenic exposure becomes a more important factor. Estimates of "total" arsenic ingested from foods and beverages often exceed the EPA oral reference dose which is based on inorganic arsenic. The assessment of risk associated with this dietary ingestion will depend on the distribution of arsenicals in various foods and their relative toxicities (i.e., arsenobetaine vs. arsenite). Efforts to estimate arsenic intakes from food compared to drinking water have been limited given the lack of databases.

The critical issue for arsenic in foods is whether the form of arsenic is organic or inorganic. Certain organoarsenicals found mainly in seafoods are considered to be virtually nontoxic (arsenobetaine) and others (e.g., methylarsonic acid, DMA) have markedly different toxicologic properties compared to inorganic arsenicals. A recent report from U.S. EPA Region 10 indicates that marine seafood contains predominately arsenobetaine while inorganic arsenic, MMA, and DMA are found at lower concentrations (U.S. EPA Region 10, 1996a). Species-specific data for arsenic (inorganic vs. organic) in food are limited. Inorganic arsenic is found in meats, poultry, dairy products and cereals, whereas the organic forms are predominantly found in fruit, vegetables, marine fish, shellfish, and seaweed (U.S.EPA, 1988a; Velez *et al.*, 1996, USEPA Region 10, 1996a). Currently systematic, comprehensive studies have not been conducted to evaluate the forms of arsenic in typical U.S. diet(s). Current market basket surveys conducted by FDA only analyze "total" arsenic (Gunderson, 1995a,b), as have the more comprehensive diet studies reported from other countries (e.g., Dabeka *et al.*, 1993). Other national exposure studies such as NHEXAS[2] do a thorough job of evaluating multimedia/ multipathway exposures; however, those studies only measure "total" arsenic. Several U.S. EPA Office of Water databases also provide useful arsenic occurrence data for drinking water which are also limited to "total" arsenic.. These databases are the National Inorganic and Radionuclide Survey (NIRS), the National Organic Monitoring Survey (NOMS) and the Federal Reporting Data System (FRDS).

[2] NHEXAS is the National Human Exposure Assessment Survey being conducted via three consortia in the United States in which one of the main goals is to evaluate total exposure and relative source contribution by analysis of chemicals of interest in drinking water, tap water, indoor and outdoor air, dust, soil, biological samples and food.

Both EPA and other federal food regulatory agencies must have improved information on toxic forms of arsenic in both specific foods as well as in the foods that comprise the normal daily diets of the U.S. population or its specific high risk subpopulations. Therefore, analytical methods must be established that perform well for both individual food items (i.e., fish) and for broader food groups and diets that represent total daily ingestion. Species-specific arsenic data on specific foods provides the EPA with an accurate risk assessment tool for supporting its regulatory activities, such as fish advisories, and to identify populations at risk. Species-specific analytical procedures for broader food groups and total daily diets will allow evaluation of information obtained in EPA's measurements programs.

Bioavailability of arsenic species from foods is a related issue. The bioavailability of inorganic arsenic from foods compared to water has not been systematically evaluated, although soluble forms of inorganic arsenic are generally assumed to be highly bioavailable (U.S. EPA, 1984). Overestimation of inorganic arsenic exposure from foods will result in overestimation of risk from arsenic in food. Another related issue is bioavailability of arsenic from soils, which can be an important issue for populations where soils have been contaminated as a consequence of agricultural or industrial activity (Bhumbla and Keefer, 1994). Soil ingestion can be an important risk factor for young children. Soil bioavailability of arsenic can be considerably lower than its bioavailability from water and is impacted by factors such as water solubility of arsenic compounds found in soil (Davis *et al.*, 1996, US EPA Region 10 1996b). The issue of bioavailability from food (and soil depending on the study population) is one that requires formal consideration in any study in which the contribution of food to total exposure is evaluated. This will be discussed in the next section.

II.4 How Can Biomarkers and Bioavailability Data Be Effectively Used To Estimate Arsenic Exposure And Uptake?

State of the Science

Arsenic levels in blood, hair, nails and urine have all been used as bioindicators of exposure. Blood arsenic is used in poisoning cases as an indicator of acute high level exposure; also poor correlations have been reported between arsenic concentration in drinking water and blood arsenic levels because arsenic is cleared rapidly from the blood. Arsenic in nails and hair are considered reliable indicators of exposures that occurred 1 to 10 months earlier, assuming that external contamination of the samples has been eliminated. However, studies that quantitatively

correlate past levels of arsenic exposure with arsenic in hair and nails are lacking and are needed for epidemiological studies.

Total urinary arsenic and speciated metabolites in urine are used as indicators of more recent arsenic exposure. It is highly desirable to determine the different arsenic metabolites (arsenite, arsenate, MMA and DMA) in urine, rather than simply using "total" urinary arsenic. Essentially nontoxic organoarsenicals (e.g., arsenobetaine) found in certain seafoods and excreted in the urine could otherwise lead to overestimation of arsenic exposure when only "total" urinary arsenic is measured (Klaassen and Eaton, 1993). A major issue that arises with the use of speciated arsenic metabolites in urine is the potential for misinterpretation of data due to the presence of MMA and DMA in urine that is not derived from the metabolism of inorganic arsenic. The issue arises because certain marine fish and shellfish, as well as seaweeds, contain both MMA and DMA which are excreted in the urine when these foods are consumed (Velez *et al.*, 1996; Le *et al.*, 1994; Buchet *et al.*, 1994, U.S.EPA Region 10, 1996a). Various means that have been used to address this issue include: obtaining diet histories from study participants, prohibiting the consumption of certain foods prior to the study, and collecting and analyzing duplicate diet samples. It has also been pointed out that further investigation is needed to identify other arsenic-containing foods in the diet and assess their effect on urinary excretion of arsenicals (Vahter, 1994).

Other than arsenic levels in hair, nails, and blood there are few biological markers of arsenic exposure. Biomarkers emerging from the research described in Chapter III have the potential to improve the sensitivity and specificity of exposure measurements. In addition, biomarkers may make it possible to determine the impacts of various factors such as genotype that could impact human susceptibility to arsenic exposures. One promising biomarker is using blood cell chromosomal mutations as an indicator of arsenic exposure.

As indicated above, the amount of each arsenic species absorbed is very important to the overall determination of risk. The bioavailability of each arsenic species found in water and food constituents is an extremely important component of determining the relative source contribution of the risks from arsenic in water vs. arsenic in diet. Bioavailability studies need to be conducted on each of the arsenic species found in the exposure media of water, soils and food.

II.5 Proposed Exposure Research

The following exposure issues are not listed based on research priority. They are listed based on the progression within the chapter. The temporal analytical needs of certain tasks has been considered in assigning priority.

Exposure Issue 1. Develop Arsenic Speciation Methodology to Separate Arsenite From Arsenate to Support Water Treatment Decisions in Large and Small Utilities.

1a. Evaluate analytical techniques for inorganic arsenite and arsenate speciation in water

The ability to speciate the valence states of inorganic arsenic may be significant because the treatment processes remove arsenate more efficiently than arsenite, and therefore, it could be beneficial to determine the oxidation state prior to devising a treatment approach for arsenic. However, in normal operation most treatment approaches will tend to convert arsenite to arsenate, and it may not be important to differentiate arsenite from arsenate routinely. This technique will help to establish the best available treatment for drinking waters which are found to contain arsenite.

1b. Evaluate sample preservation techniques for arsenic species

The preservation of the individual arsenicals from sampling to detection is a concern in all aspects of the analytical methods. Preservation is not listed as a subtask within other issues but it should be understood that it is of primary concern within all speciation based analysis.

(1a Medium Priority, 1b High Priority)

This research will support decision making to evaluate the best available treatment technology and provide analytical monitoring capability for MCL compliance. Development of analytical methods for water will provide the technological basis for proceeding with development of methods for analysis of more complex matrices.

Exposure Issue 2. Develop Extraction Methods for Inorganic and Organic Arsenicals in Foods to Allow for the Separation and Detection of Individual Arsenic Species in Foods.

The primary need is for analytical methods that will allow measurement of the inorganic and organic fractions of arsenic in food. A secondary priority is the ability to distinguish the specific organic forms (e.g., MMA and DMA) that may be of toxicological concern.

2a. Methods for speciation in target food items (e.g., seafood)

The ability to speciate arsenic in certain foods provides the EPA with an accurate risk assessment tool for supporting its regulatory activities, such as fish advisories. Speciation based methods are required to identify foods and food groups that are associated with the more toxic forms of arsenic so that exposure evaluations accurately reflect the relative importance of foods as compared to other media and exposure pathways. (High Priority)

2b. Methods for speciation in composite daily diet (i.e., duplicate diets)

EPA measurements of total human exposure from multiple pathways requires collecting, compositing and analyzing 24-hour duplicate diet samples for direct comparisons of dietary exposure to other concurrent pathways of exposure. Speciation-based analysis will allow for small population exposure assessments which accurately quantify the risk associated with diet. The ability to speciate the arsenic in duplicate diet samples will also provide the basis for assessing the bioavailability of ingested arsenic. (Medium Priority)

2c. Impact of food preparation on the distribution of individual arsenicals

Develop methodologies to evaluate the effects of preparation and cooking on the distribution of arsenicals in ready-to-consume foods. The thermal and chemical environments that the organic and inorganic arsenic species are exposed to during cooking may cause an interconversion of the arsenic species. (Medium Priority)

These research areas will address the relative source contribution of arsenic ingestion via diet and improve mass balance data for humans including all ingestion routes. This information could be useful in Effects Issue 3a. Research and development of species specific analytical methods must be shared by EPA and other federal food regulatory agencies such as FDA and USDA. EPA research should focus on the analytical procedures that directly support its programs, namely evaluation of dietary intake in ORD total human exposure monitoring programs and risk evaluations for regulatory programs.

Exposure Issue 3 Development of Arsenic Speciation Methodologies in Biological Matrices to Support Exposure Assessment, Bioavailability, and Biomarker Research.

3a. Refine and evaluate an analytical approach for the separation of arsenite, arsenate, MMA, DMA and arsenobetaine in urine

3b. Refine and evaluate an analytical approach for the separation of arsenite, arsenate, MMA, DMA, and arsenobetaine in blood

3c. Refine and evaluate analytical approaches for speciation of arsenic to support bioavailability investigations

3d. Refine and evaluate analytical approaches for speciation of arsenic in tissues

The capability of speciating arsenic in biological fluids provides a means of monitoring recent exposures to arsenic. This speciated information may indicate the source of the exposure, for instance, high arsenobetaine concentration may indicate a diet high in seafood. The ability to speciate arsenic in all exposure routes provides a unique capability to address the bioavailability of the arsenic from the various routes. In addition, this speciation information can be used in identifying a biomarker for arsenic.
(3a High Priority, 3b,3c,3d, Medium Priority)

In pharmacokinetic and mechanistic studies of arsenic, it will be important to be able to distinguish between inorganic arsenic, MMA and DMA. Ideally, analysis would also differentiate between arsenite and arsenate, although this may be more difficult to achieve and is therefore a longer term priority. Current toxicological studies are proceeding with the use of radio-labeled arsenic; the eventual availability of non-radio-labeled species-specific methods for biological matrices will be a valuable research tool. These areas have been identified by AWWARF 1995 as high priority projects in arsenic research. The priority assigned above is an indicator of short term analytical achievability and the use of urine as a primary arsenic exposure indicator.

Exposure Issue 4 Development of Liquid and Solid Species Specific Standard Reference Material for Arsenic in Water, Foods, Urine, and Tissues.

4a. Refine and evaluate a standard reference material for foods which provides species specific concentrations of arsenic

4b. Refine and evaluate a standard reference material for biological tissues which provides species specific concentrations of arsenic

4c. Refine and evaluate a standard reference material for water, blood and urine which provides species specific concentrations of arsenic

The development of standard reference materials (SRM) for arsenic which are species specific is an area of research which is fundamental to all speciation based analytical methodology. This research will provide the analytical community the capability of evaluating the developed methodologies accuracy in terms of species specific concentration and provides a means of assuring species specific integrity .
(4b Medium Priority, 4a, 4c High Priority)

This research area will provide the necessary QA/QC materials for speciation based exposure assessment. This research will be conducted primarily by NIST and NRCC. The priority assignments are made based on analytical feasibility and temporal consistency with Exposure Issue 3 and Exposure Issue 2.

Exposure Issue 5 Dietary Exposure Assessment Studies for Populations with High Dietary Intake of Foods Associated with Toxic Species of Arsenic.

5a. Dietary exposure assessment studies of arsenic species for typical U.S. diets and highly exposed sub-populations

High dietary "total" arsenic exposure can occur because of low levels of arsenic in many foods consumed or because of very high levels in a few foods. The later is usually associated with unique populations whose dietary habits differ from the norm. Studies are needed to evaluate the species of arsenic in the array of foods in the typical U.S. diet and to identify diets containing high levels of the toxic forms of arsenic. The amount and variability of exposure from food and beverages needs to be quantified for various populations, taking into account demographic characteristics. This could be accomplished by modeling and/or by direct measurement. Neither procedure can be accomplished until analytical methods for speciation of foods are available and a database is created on species-

specific arsenic levels in foods. Modeling will utilize species-specific information for food groups and items combined with information on dietary consumption to identify high risk populations. Measurements consistent with market basket collections of the foods consumed by the U.S. populations and specific high risk subpopulations will be used in this modeling. Inclusion of biomarkers in these studies will aid in addressing the species specific adsorption rates of arsenic from ingested food.
(High Priority)

This research will address relative source contribution issues with dietary ingestion of arsenic while targeting subpopulation which may have evaluated risk factors associated with dietary ingestion. This information may be helpful in future epidemiology studies. This is consistent with Exp. Task 4a.

Exposure Issue 6 Development of National Database on Arsenic Occurrence and Concentrations in Water, Soil and Dietary Constituents for Use in Epidemiological Studies and Agency Regulatory Activities.

6a. Development Of A National Database On Arsenic Occurrence And Concentrations In Water, Soils, and Dietary Constituents.

Present databases do not report occurrence and concentrations of arsenic by species in the various media. Also, large amounts of the data on arsenic in drinking water only report arsenic levels that exceed the current MCL of 50 µg/L. As speciation and low-level arsenic detection data continues to be developed in water supplies, soils and diet, there will be a need to assemble this evolving data into a national database on arsenic. This work will act as a refinement of the near-term need to evaluate the currently available databases for use in epidemiological studies and Agency risk assessments/risk characterizations/risk management activities. This work is of lower immediate priority because it relies on the development and implementation of other research before being feasible.
(Low Priority)

Exposure Issue 7. Biomarkers of Exposure in Biological Media

7a Development of biomarkers of exposure in biological media for use in epidemiological studies

The exposure in most drinking water epidemiological studies has been based on the analytical methods for speciation of foods are available and a database is created on species-

before 1970 to measure arsenic have questionable precision at low concentrations. The use of biomarkers of exposure that would potentially measure the dose and reduce misclassification bias would be desirable in epidemiological studies. Development of these biomarkers tools will improve the precision of the risk estimate.
(High Priority)

This exposure issue is related to the analytical development of speciation in Exposure Issue 3a and the QA/QC Exposure Issue 4c. The support of future epidemiology within this exposure issue is related to Effects Issue 2a and 3a.

Exposure Issue 8. Bioavailability of Arsenic

8a Conduct research to determine the bioavailability of all arsenic species found in water, soils and food constituents

Arsenic species are only a systemic risk if the ingested arsenic is absorbed from the gastrointestinal tract in a form that is biologically relevant. The question of how much inorganic arsenic vs. organic arsenic found in urine came from the exposure media and how much is a result of biotransformation in the body is also important for assessing exposure risks. Bioavailability studies using newly evolving analytical techniques to speciate arsenic will greatly enhance our ability to assess the relevant risks from each arsenic containing media and allow for more precise estimation of the relative source contribution that arsenic levels in water have to the overall arsenic exposure. The priority of the research is Medium for the near-term because the analytical methods are not available and need to precede this research.
(Medium Priority)

TABLE II.1 EXPOSURE RESEARCH STRATEGY MATRIX FOR ARSENIC

ISSUE	TASK	PRODUCT	USE
EXP. Issue 1. Develop arsenic speciation methodology to separate As(III) from As(V) to support water treatment decisions in large and small utilities.	Exp. Task 1a. Evaluate analytical techniques for Inorganic As(III) and As(V) speciation in water. Medium Priority	As speciation method for drinking water	Treatment evaluation in NRMRL, individual water treatment plant, AWWA
	Exp. Task 1b. Evaluate sample preservation techniques for Arsenic species. High Priority	Preservative for Arsenic speciation methods	Application to all speciation based methods
EXP. Issue 2. Develop extraction methods for inorganic and organic arsenicals to allow for the separation and detection of individual arsenic species in foods.	Exp. Task 2a. Speciation in target food items (i.e. seafood). High Priority	As speciation method and improved information on As species for target foods/groups	Exposure assessment by NCEA, NERL, FDA, USDA, OW
	Exp. Task 2b. Speciation in composite daily diet (i.e. duplicate diets). Medium Priority	As speciation method to determine inorganic forms in composite samples	Exposure assessment by NCEA, NERL, FDA, USDA
	Exp. Task 2c. Impact of food preparation on the distribution of individual arsenicals. Medium Priority	Improved information on As speciation for prepared foods	Exposure assessment by NCEA, NERL, FDA, USDA

ISSUE	TASK	PRODUCT	USE
EXP. Issue 3. Development of arsenic speciation methodologies in biological matrices to support exposure assessment, bioavailability, and biomarker research.	Exp. Task 3a. Refine and evaluate an analytical approach to the separation of As(III), As(V), MMA, DMA and Arsenobetaine in urine. High Priority	Analytical method capable of separating inorganic arsenic III from MMA, DMA and arsenobetaine in urine	Support of exposure monitoring and bioavailability studies in NHEERL or NCEA, NIOSH
	Exp. Task 3b. Refine and evaluate an analytical approach to the separation of As(III), As(V), MMA, DMA and Arsenobetaine in blood. Medium Priority	Analytical method capable of separating inorganic arsenic III from MMA, DMA and arsenobetaine in blood	Support of exposure monitoring and bioavailability studies in NHEERL or NCEA, NIOSH
	Exp. Task 3c. Refine and evaluate analytical approaches to speciate arsenic to support bioavailability investigations. Medium Priority	Speciation method in a variety of sample types foodstuffs, drinking water, biologicals	Analytical support for bioavailability studies
	Exp. Task 3d. Refine and evaluate analytical approaches to speciation in tissues. Medium Priority	Speciation method for tissue samples.	Non-radio based analytical support for NHEERL
EXP. Issue 4. Development of liquid and solid species specific standard reference material (SRM) for arsenic in water, foodstuffs, urine, tissues.	Exp. Task 4a. Develop a SRM for foods which provide species specific concentrations of arsenic High Priority	SRM to evaluate methods development in food	NERL, Method validation for NCEA exposure assessment, EPA, FDA, USDA, NIST, OW
	Exp. Task 4b. Develop a SRM for biological tissues which provides species specific concentrations of arsenic Medium Priority	SRM to evaluate methods development in tissues	NERL, Method validation for NCEA exposure assessment, EPA, NIOSH, NIST

ISSUE	TASK	PRODUCT	USE
	Exp. Task 4c. Develop a SRM for water, blood and urine which provides species specific concentrations of arsenic High Priority	SRM to evaluate methods development in water, blood and urine	NERL, Method validation for NCEA exposure assessment, EPA, NIOSH, NIST
EXP. Issue 5. Dietary exposure assessment studies which address a selected populations exposure to arsenic from a high dietary intake or target food groups.	Exp. Task 5a. Dietary exposure assessment studies of arsenic species in the typical U.S. diet and highly exposed sub-populations. High Priority	Database on speciated arsenic in typical U.S. foods and for diets of targeted highly exposed populations.	National and Regional arsenic diet data for improved EPA risk assessments and risk management decisions. FDA and USDA will also utilize these data.
EXP. Issue 6. Development of National Database on arsenic occurrence and concentrations in water, soil and dietary constituents for use in epidemiological studies and Agency regulatory activities.	Exp. Task 6a. Development of an National Database on arsenic occurrence and concentrations in water, soils, and dietary constituents Low Priority	National Database on Speciated Low-Level arsenic levels in water, soils and dietary constituents	Arsenic exposure information for epidemiological studies and for Agency risk assessment/risk management activities
EXP. Issue 7. Biomarkers of Exposure in Biological Media	Exp. Task 7a. Development of biomarkers of exposure in biological media for use in epidemiological studies. High Priority	Standardized biomarkers to assess exposure or arsenic species from various media.	Standardized biomarkers protocols will be used for assessing exposures in epidemiological studies and for improving the precision of the risk assessments
EXP. Issue 8. Bioavailability of Arsenic	Exp. Task 8a. Conduct research to determine the bioavailability of all arsenic species found in water, soils and food constituents. Medium Priority.	Empirically derived bioavailability (oral absorption) factors will be determined for each arsenic species from water, soils and various food constituents.	Improvements in the quantitative precision of the arsenic risk assessments and improvements in the determination of the relative source contribution of arsenic in water vs. Arsenic in other exposure media.

TABLE II-2: EXPOSURE TASK SUMMARY, CURRENT ACTIVITIES AND PROPOSED SEQUENCE FOR STUDIES

	Task Type[1]	On-going	Priority	TIME FRAME[2]					
Task - Short Study Title	**I**	**E/O**	**Y/N**	**Priority**	**FY97**	**FY98**	**FY 99**	**FY00**	**FY01**	**FY02**
Exp. Task 1a. Evaluate analytical techniques for Inorganic As(III) and As(V) speciation in water	I		Y	Medium	EPA	EPA				
Exp. Task 1b. Evaluate sample preservation techniques for Arsenic species	I		Y	High	EPA	EPA				
Exp. Task 2a. Speciation in target food items (i.e. seafood)	I	E	N	High	X	X	X	X	X	
Exp. Task 2b. Speciation in composite daily diet (i.e. duplicate diets)	I	E	N	Medium		X	X	X	X	
Exp. Task 2c. Impact of food preparation on the distribution of individual arsenicals.	I	E	N	Medium		X	X	X		
Exp. Task 3a. Refine and evaluate an analytical approach to the separation of As(III), As(V), MMA, DMA, and Arsenobetaine in urine	I		Y	High	EPA	EPA				

1 I=Intramural (EPA inhouse research), E=Extramural (EPA sponsorship through grant or coop), O=other governmental or private entities will need to plan and fund

2 EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort

X = EPA resources insufficient to address these tasks, need external research effort

Task - Short Study Title	I	E/O	Y/N	Priority	FY97	FY98	FY 99	FY00	FY01	FY02
Exp. Task 3b. Refine and evaluate an analytical approach for the separation of As(III), As(V), MMA, DMA and Arsenobetaine in blood	I	E	N	Medium		X	X			
Exp. Task 3c. Refine and evaluate analytical approaches to speciate arsenic to support bioavailability investigations	I	E	N	Medium				X	X	X
Exp. Task 3d. Refine and evaluate analytical approaches to speciate arsenic in tissues	I	E	N	Medium		X	X			
Exp. Task 4a. Develop a standard reference material for foods which provide species specific concentrations of arsenic		O	N	High	X	X	X			
Exp. Task 4b. Develop a standard reference material for biological tissues which provides species specific concentrations of arsenic		O	N	Medium	X	X	X			
Exp. Task 4c. Develop a standard reference material for water, blood and urine which provides species specific concentrations of arsenic		O	N	High	X	X	X			
Exp. Task 5a. Dietary exposure assessment studies of arsenic species for typical U.S. diets and high exposed sub-populations	I	E	N	High				X	X	X
Exp. Task 6a. Development of an National Database on arsenic occurrence and concentrations in water, soils, and dietary constituents	I	E	N	Low			X	X	X	X

Task - Short Study Title	I	E/O	Y/N	Priority	FY97	FY98	FY 99	FY00	FY01	FY02
Exp. Task 7. Development of Biomarkers of Exposure in biological media for use in epidemiological studies	I	E	Y	High	EPA	EPA				
Exp. Task 8. Conduct research to determine the bioavailability of all arsenic species found in water, soils, and food constituents	I	E	N	Medium		EPA	EPA	EPA		

CHAPTER III
HEALTH EFFECTS:
HAZARD IDENTIFICATION AND DOSE-RESPONSE

III.1 Background

This chapter discusses the research questions that address hazard identification and dose-response assessment associated with arsenic exposure. Hazard identification research involves the development of methods that demonstrate a qualitative relationship between exposure and effect. Dose response research then characterizes this relationship to link dose with incidence and severity of effect considering the mechanism(s) by which arsenic exerts its toxicity. Factors that influence dose response are also evaluated. This information is then used to develop quantitative models for estimating risk. The arsenicals discussed here include inorganic and organic forms.

III.2 What are the health effects associated with arsenic exposure?

Unlike most environmental contaminants, there is a large human database available for inorganic arsenic. Ingestion of inorganic arsenic can result in both carcinogenic and noncarcinogenic effects. Epidemiologic investigations have reported as association between arsenic exposure in drinking water and cancer. This effect has not been demonstrated in arsenic ingestion studies with animals. Thus, we lack a comparable model system for studying arsenic induced carcinogenicity. While there is a substantial human database for inorganic arsenic, there is considerable debate among the scientific community over the interpretation of these data and their application in risk assessment. Experimental data on the effects of organic forms of arsenic are not as well characterized and thus may be a subject for future research. Limited data in animals indicate that some organic forms of arsenic also produce cancer and noncancer health effects.

State of the Science

Available information on the health effects of inorganic arsenic and other arsenic species has been discussed in several documents (U.S. EPA, 1988, 1993, ATSDR, 1993).

Carcinogenic effects in humans

Epidemiological studies conducted in several countries including Taiwan, Mexico, Chile, Hungary, England, Japan and Argentina have reported an increased incidence of skin cancer in exposed populations (Tseng *et al.*, 1968; Chen *et al.*, 1986; Cebrian *et al.*, 1983; Tsuda *et al.*, 1990; and Cuzick *et al.*, 1992) Several of these studies have also reported and analyzed an association between inorganic arsenic ingestion and increased mortality from internal cancers such as liver, bladder, kidney, and lung (Chen *et al.*, 1986; Tsuda *et al.*, 1990; Hopenhayn-Rich *et al.*, 1993; and Smith *et al.*, 1992). Studies conducted in the U.S. have not demonstrated an association between inorganic arsenic in drinking water and skin cancer. The U.S. studies had very little power, however, to detect the effects of concern.

The largest epidemiology study is the Taiwan study (Tseng *et al.* 1968), which also serves as the basis for the current EPA cancer risk assessment. In this study, an increased prevalence of skin cancer was observed among approximately 40,000 Taiwanese consuming arsenic contaminated water (up to 1,200 µg/l arsenic) from artesian wells as compared with approximately 7,500 residents from Taiwan and a neighboring island, Matsu, consuming "arsenic free" (0-17 µg/l arsenic) water. The number of people with skin cancer was reported to increase with increasing concentrations of arsenic in the water they consumed. Several strengths and uncertainties associated with this study and the resulting arsenic risk assessment are discussed in Chapter 1.

Future epidemiological studies should be designed to improve exposure analysis, provide information on arsenic speciation, reduce confounding and bias and utilize biomarkers if possible. Use of biomarkers can help reduce uncertainty in the interpretation of epidemiological studies. In a long term research plan, biomarkers identified from mechanistic research in experimental model systems can be used to help design future epidemiology studies to improve the sensitivity and specificity of exposure measurements (see also Chapter II), provide insight into the shape of the low-level dose response curve and provide plausibility of biological effect. In addition, biomarkers may make it possible to determine the impact of various factors such as genotype that could impact human susceptibility to arsenic exposures.

Based on current information, biomarkers such as hyperkeratoses and chromosomal mutations in blood cells of humans are technically feasible and may offer the greatest potential for success. Additional biomarkers may include DNA methylation (see mechanism section, below).

Ongoing EPA Research

Currently, EPA is conducting a cohort mortality study on approximately 4,000 individuals in Utah. Individuals living in areas with historically high background levels of arsenic will be compared with others living in an area where arsenic concentrations fall within the MCL limit for arsenic. Specific cause of death for cohort members will be compared with deaths for the State of Utah. The cohort was originally ascertained through the historic Mormon Church (Church of Jesus Christ of Latter-day Saints) records. Due to the Mormon lifestyle, risk factors such as smoking, second hand smoke, and alcohol consumption are expected to be minimal. This U.S. study may add to the weight of evidence determination for arsenic and provide insight as to the feasibility of evaluating the incidence of important toxic and carcinogenic endpoints such as cardiovascular effects and internal cancers.

EPA is also developing a report that will describe the feasibility of conducting epidemiologic studies in the U.S. that will contribute to an improved quantitative risk assessment of the health effects of arsenic in drinking water. This will include a description of possible study sites, numbers of individuals exposed, levels of exposure, and preliminary power calculations concerning the feasibility to evaluate different health endpoints such as cardiovascular, reproductive, dermatologic and cancer.

Along with these studies, EPA is conducting studies on arsenic urinary metabolic profiles. This project will provide information on baseline data at exposures typically found in the U.S.. Diet as a source of exposure will be examined along with variability of arsenic metabolic profiles in individuals. It is hoped that the information gained from this study will facilitate the standardization of biomarkers for susceptibility and effect for arsenic that can be used in future epidemiology studies. Biomarker use could also provide insight into possible mechanisms for arsenic induced toxicity and carcinogenicity and facilitate development of pharmacokinetic models relating exposure with effects in humans (see below).

Finally, EPA is collaborating with ongoing investigations in other countries such as Chile and India to evaluate the internal carcinogenic and dermatologic effects of arsenic exposure in drinking water. Results from these studies will provide further information on dose response that can be used in the near term to refine the arsenic risk assessments.

Carcinogenic effects in animals

There is limited evidence of inorganic arsenic-induced carcinogenicity in animal studies. Standard experimental animal models do not demonstrate the carcinogenic effects of arsenic seen in humans. Although there appears to be a lack of an animal model that reproduces the carcinogenic effects in humans, there are emerging animal models such as transgenic mice that may have utility for arsenic effects research.

There are also limited data concerning the carcinogenic effects of organic arsenic forms in animals. A slight increase in pancreatic tumors was observed in male rats following oral exposure to 4-hydroxy-3-nitrobenzene arsonic acid or roxarsone (NTP, 1989). Male rats that had been initiated with diethylnitrosamine and then exposed to dimethylarsinic acid (DMA) had an increased incidence of basophilic foci (a precancerous lesion) in the liver, suggesting that DMA could be a promoter (Johansen *et al.*, 1984; see also discussion in mechanisms section, below). A few studies indicate that organic arsenicals, DMA and roxarsone, may be able to cause mutations and DNA strand breaks (ATSDR, 1993).

Other data related to carcinogenicity

From studies conducted in animals, it can be concluded that inorganic arsenic is a genotoxic agent. Experimental evidence suggests that inorganic arsenic does not act to damage DNA directly as a point mutagen, but produces damage at the chromosomal level inducing chromosomal aberrations, micronuclei and sister chromatid exchange in mammalian cells, and neoplastic transformations in Syrian hamster embryo cells. Although arsenic doesn't appear to cause point mutations, based on the available data, it does cause damage to DNA as noted above (ATSDR, 1993; EPA, 1993). The mechanism(s) for these effects is not known at present. Depending on the mode of action, the mechanism could be linear or nonlinear.

Ongoing EPA Research

Research efforts have been initiated to develop an animal model for testing arsenic-induced carcinogenesis using genetically altered mice. P53 knockout mice will be exposed to 4 arsenic species in drinking water: sodium arsenite and sodium arsenate, monomethyl arsonic acid (MMA)

and DMA. This limited study will evaluate the animals for the presence of common cancer lesions. Results from this study will be used in the development of an animal model and could allow for a better understanding of mechanism from the determination of the active form of arsenic in arsenic carcinogenesis. Other studies on carcinogenesis focus on the actions of arsenicals in multistage carcinogenesis, an evaluation of arsenic as a tumor promoter, interactions between arsenic and genetic material (DNA methylation) and the mechanistic aspects associated with variations in susceptibility within the human population.

Noncarcinogenic effects in humans

Exposure to inorganic arsenic has also been reported to result in adverse effects other than cancer in humans. Dermal changes including variations in skin pigments, thickening of skin (e.g., hyperkeratosis) and ulcerations, peripheral neurotoxicity (e.g., tingling and loss of feeling in arms and legs) and auditory nerve damage, peripheral vascular and cardiac effects, goiter, gastro-intestinal and liver effects, developmental toxicity, and diabetes have been observed. These effects are seen at various levels in the range of exposures reported in the epidemiology studies (U.S.EPA, 1993; ATSDR, 1993).

In humans, acute oral poisoning with inorganic arsenic leads to gastrointestinal irritation accompanied by difficulty in swallowing, thirst, abnormally low blood pressure, and convulsions (Gorby, 1994). Both acute and chronic exposures to inorganic arsenic result in capillary damage to target tissues which exacerbates the damage observed in these tissues (Clarkson, 1991). Signs of chronic exposure to arsenic in drinking water are dermal changes such as variations in skin pigments, hyperkeratoses, and ulcerations. Blackfoot disease, a peripheral vascular disease leading to peripheral tissue necrosis, has been observed in humans consuming arsenic contaminated drinking water in Taiwan (Tseng *et al.*, 1968) and India (Bagla and Kaiser, 1996). Human studies have reported peripheral and central neurologic effects after exposure to inorganic arsenic (Morton and Dunnette, 1994). Enlargement of the liver was noted in populations in India. Ischemic heart disease and diabetes were observed in Taiwanese where Blackfoot disease is endemic.

Some human studies have reported an association between arsenic exposure and adverse reproductive outcomes and developmental impacts (Rogers, 1996). The types of effects noted in occupationally exposed humans include spontaneous abortion, congenital malformations and low

birth weight. Exposure to inorganic arsenic was associated with decreased maternal blood glutathione levels indicative of maternal oxidative stress.

When considering the range of noncancer effects associated with inorganic arsenic exposure, hyperkeratosis observed in the Taiwanese population (Tseng *et al.*, 1968) is considered the most sensitive endpoint of toxicity and serves as the basis for EPA's current noncancer risk assessment.

Noncarcinogenic effects in animals

Signs of acute arsenic poisoning in animals include vomiting and diarrhea, weakness, trembling, tachycardia and collapse (U.S. EPA, 1993). Like humans, target organs appear to include liver, kidney, and the developing organism.

In animal studies, arsenite and arsenate are more developmentally toxic than the methylated, organic forms (Willhite, 1981). Types of malformations observed include exencephaly, encephalocele, cleft palate and lip, and malformations of the eye and ear, skeleton, kidney and urogenital system as observed in hamsters, mice, rats and rabbits (Rogers, 1996). *In vivo* studies in animal models indicate that these teratogenic effects are not secondary to maternal toxicity (Golub, 1994). There is some evidence to support a variety of different mechanisms, similar to those associated with carcinogenicity, including alteration of DNA methylation, inactivation of methyltransferases, modulation of protein phosphorylation and production of reactive oxygen species. Significantly, the dose–response relationships for arsenite and arsenate are very different, and recent evidence suggests that the mechanisms responsible for induction of malformations may be different.

Limited toxicity data on organic forms of arsenic suggest that irritation of the gastrointestinal tract, mild effect on liver, tubular damage to kidneys and some neurological effects may result following oral exposure in animal studies. The limited nature of these data make it difficult to quantitatively compare these effects with those resulting from inorganic arsenic exposure (ATSDR, 1993).

Ongoing EPA Research

EPA is conducting several developmental toxicity studies that evaluate of the effects of metals, such as zinc and selenium, and antioxidants on the prevention of arsenic-induced malformations and the mechanisms related to arsenic-induced malformations. This line of research addresses questions related to mechanism(s) of action and modifiers of susceptibility that could impact the assessment of risk for potentially sensitive members of the population. Further, these data may provide dose response information for effects other than cancer.

III.3 What are the characteristics of dose-response for various toxic endpoints?

State of the Science

Arsenical doses associated with the effects previously described are summarized in ATSDR (1993) and U.S. EPA (1993). In general, doses of 2,000 µg/kg arsenic have been reported to be lethal in humans. A dose of 1,000 µg As/kg/day for a one week exposure resulted in frank effects on liver, kidney, stomach, nervous system. Longer term exposure at much lower doses (<80 µg As/kg/d) produced cardiovascular, neurological, dermatologic, hepatic and renal effects. Cancer resulted from long term exposures to doses of 9 to 40 µg As/kg/day.

As noted above, the Taiwan epidemiologic study serves as the basis for the EPA cancer and noncancer dose response assessments. In this study, an ambient arsenic concentration of less than 17 µg/l (1 µg As/kg/d) was considered a no-effect level. Arsenic concentrations of 17-770 µg/l (0.8 - 14 µg As/kg/d) were associated with skin and vascular lesions. These dose response data were used to derive the noncancer risk assessment described in Chapter 1.

Pharmacokinetic and biologically based-models

The shape of the dose response curve for arsenic-induced cancer and noncancer effects relating the range of observation to the range of extrapolation is a source of uncertainty in arsenic risk assessment. This uncertainty influences both selection of a dose response model and high to low dose extrapolation. There are several factors that can influence dose response, including metabolism, tissue dosimetry, mechanism of action and other factors that may modify toxicity and individual susceptibility. Arsenic undergoes a complex cycle of oxidation and reduction in humans

and other species. This cycling is a well known mechanism for toxicity and carcinogenicity. Tissue dosimetry provides a link between exposure and dose response assessment (see Figure 1 in the Introduction). The development and validation of physiologically based pharmacokinetic (PBPK) models can serve as a tool for making this link. Development of PBPK models using human data where possible can provide insight into the kinetics of substances such as arsenic in humans through a quantitative, biologically based description between exposure and target tissue dose of the active chemical species. This is particularly important because there are multiple target tissues (e.g., skin, lung, liver, bladder, kidney), and the target tissue dose of arsenate, arsenite and their methylated metabolites is a balance between competing processes of reduction, methylation, binding, and excretion. Additional advantages of these models include the evaluation of different exposure scenarios on cumulative tissue dose and body burden, helping to prioritize areas for further study, providing a link with other models (biologically-based dose response (BBDR) models) to assess toxicological effects, and studying the impacts of a variety of host factors on toxicity in humans.

The evaluation of the dose response relationship for arsenic-induced carcinogenicity is somewhat hindered by the lack of an appropriate animal model. Where appropriate human data are not available, there may be potential to utilize animal models or other laboratory models to understand dose–response relationships for arsenic induced health effects. For some adverse effects, studies in animal models can provide evidence to confirm the effects associated with arsenic exposure in human epidemiologic studies, and thus also provide a basis for mechanistic research.

Research with laboratory model systems can also facilitate the dose response evaluation of noncancer effects such as developmental toxicity described above or in the area of vascular effects. For example, recent *in vitro* work with cultured human vascular endothelial cells suggests that the arsenic-induced cardiovascular effects could arise from toxicant induced injury to vessel walls (Chen *et al.*, 1990; Chang *et al.*, 1991). Development of animal models to study dose dependency and mechanistic aspects of these and other noncancer effects would complement epidemiological evaluations for noncancer effects and subsequent dose response evaluations.

Further discussion on the role of mechanism and modifiers of susceptibility in dose response is given below.

Ongoing EPA Research

Current EPA research efforts focus on improving our understanding of arsenic metabolism, factors that may influence arsenic metabolism, arsenic methylation and research that will support the development of a PBPK model for humans. Mechanistic research combined with information from metabolism studies and studies evaluating the modification of toxicity and susceptibility can eventually be used in the development of a BBDR model. This information can improve risk estimation for arsenic induced toxicity and carcinogenicity by improving our understanding of "dose."

III.4 What are the mechanisms associated with arsenic carcinogenicity and toxicity?

State of the science

Mechanistic research conducted to refine arsenic risk assessment encompasses the range of events from exposure to target tissue dose associated with adverse health effects and can impact all phases of risk assessment, particularly dose response. A major challenge in this area is the limitation in sensitivity and specificity of current analytical techniques used to measure arsenicals in tissues, body fluids and other media (see Chapter II). This has had a major impact on pharmacokinetic and toxicological mechanistic studies because it is difficult with current methodologies to extract and distinguish between arsenite and arsenate and their metabolites in biological and environmental samples. This is important because different forms of arsenic exhibit differences in disposition and toxicity, and they act by different mechanisms at the biochemical level.

It has long been known that inorganic arsenate is reduced to arsenite and subsequently methylated to form MMA and DMA in humans and experimental animals. The methylated metabolites of arsenic are also the predominant forms excreted in the urine of most species. Historically, the operative assumption has been that arsenite is the active or carcinogenic form of arsenic and that methylation is simply or solely a mechanism of detoxification and excretion. The basis for this assumption is that the methylated forms of arsenic are far less acutely toxic than either arsenite or arsenate (ATSDR, 1993).

Until lately, there were no studies that had directly tested the assumption of methylation as a simple detoxification mechanism. However, DMA has recently been shown to increase the enzyme activity of a rat kidney enzyme, ornithine decarboxylase (ODC) (Yamamoto *et al.*, 1995), which serves as a biological indicator of cell proliferation and promoter activity (Brown and Kitchin, 1996). In addition, arsenite, itself, has been shown to produce a dose dependent increase in rat liver ODC activity. DMA has also been demonstrated to be a promoter of cancer in multiple organs such as urinary bladder, kidney, liver, and the thyroid in rats and in lungs of mice (Yamamoto *et al.*, 1995, Yamanaka *et al.*, 1996). Considering this and other information, its been postulated that arsenic may act as a promoter rather than an initiator of carcinogenesis and affect some but not all elements of multistage carcinogenesis (Brown and Kitchin, 1996). Epidemiological evidence that arsenic acts at a later stage in the development of cancer, as noted with increasing risk of lung cancer mortality with increasing age of initial exposure, independent of time after exposure ceased (Brown and Chu, 1983), supports the hypothesis that arsenic acts as a promoter of carcinogenesis. Further studies are needed to clarify the mechanism of arsenic carcinogenesis and study the dose response of arsenical promotion. These studies provide insight on the nature of the dose response relationship for arsenic carcinogenicity and the role of methylation as a detoxification mechanism.

The mechanism for arsenical carcinogenesis may be related to the major route of biotransformation. Arsenic is methylated by an arsenic methyltransferase utilizing S-adenosylmethionine (SAM) as the methyl donor. Arsenic may perturb the utilization of methyl donor groups needed for normal DNA methylation by interacting with the substrate, SAM, or various enzymes, methyltransferases. Depending on the conditions, this perturbation could result in hypo- or hypermethylation of DNA. High doses of arsenic were thought to compete for the methyl donor pool during detoxification, leading to hypomethylation (Mass, 1992). Since arsenic interacts with methyltransferases, it may inhibit or enhance other methyltransferases that could lead to hypermethylation. Mass and Wang (in press) found that exposure to arsenite and to a lesser extent, arsenate, but not DMA, produced significant hypermethylation of cytosine residues in the 5' promoter region of the p53 tumor suppressor gene in human lung adenocarcinoma cells. They postulated that this hypermethylation could result in suppression of the expression of tumor suppression genes and lead to cancer. An effect of arsenic on p53 or some other tumor suppressor gene by alteration of DNA methylation provides a heritable mechanism whereby arsenic appears to act as a nongenotoxic agent. Yet inhibition of tumor suppressor gene function (or even enhancement of oncogene expression) is known to lead to genetic instability. This would endow

arsenic with properties of both a genotoxic and nongenotoxic agent; it would also provide a mechanism whereby arsenic can act as an initiator or promoter/progressor.

Additional considerations for arsenic methylation include saturation of this enzyme process in humans and the effects of preexisting disease on the capacity for humans to methylate arsenic. Methylation of arsenic is an enzymatic process and thus can be limited by saturation. Saturation of arsenic methylation has been suggested as a hypothesis for low dose nonlinearity (EPA, 1988; Petito and Beck, 1991; Carlson-Lynch *et al.*, 1994). There is uncertainty, however, regarding the dose at which saturation might occur. Other researchers have concluded that the data do not support a threshold for methylation (Hopenhayn-Rich *et al.*, 1993; Smith *et al.*, 1995).

In an evaluation of Taiwanese populations, Hsueh *et al.*, (1995) identified chronic liver disease as a risk factor that increases the development of skin cancer. In a separate study comparing healthy individuals to those with liver disease, it was noted that preexisting disease did not change the cumulative excretion of arsenic in urine but did alter the ratio of the MMA and DMA metabolites (Buchet *et al.*, 1984; Geubel *et al.*, 1988). Studies in animals suggest that liver disease may reduce the availability of the methyl donor group, SAM, necessary for arsenic methylation.

Ongoing EPA Research

Mechanistic research on arsenic carcinogenicity and toxicity at EPA focuses on arsenic methylation and the enzymes involved in that process. This includes the interaction between arsenic and DNA methylation which could explain whether arsenic suppresses expression of certain genes from their function. Questions on whether arsenic acts as a carcinogenic promoter are also being addressed. With respect to noncancer effects, the mechanism by which arsenic perturbs the cell cycle and induces cell death is being investigated in animal embryos. Information from these studies will reduce the uncertainty in selection of dose response models for cancer and developmental effects. Mechanistic information will also be of use in the development of a BBDR model.

III.5 What are the modifiers of human susceptibility?

State of the science

The response to arsenic exposure can be modified by the characteristics of the exposed organism. These modifiers can range from environmental factors to those that are characteristic to the organism. Environmental factors include diet or concurrent exposure to other toxicants. Diet and other environmental factors can affect arsenic methylation. Methylation of arsenic requires the availability of a methyl group donor, (SAM). A low protein diet or diet deficient in the amino acid methionine can result in decreased availability of SAM. (However, a low fat diet is also considered to lower the risk for developing some forms of cancer.) Further, diets low in cysteine, choline, folate, and vitamin B12 can minimize the methyl groups available for transmethylation (Montgomery *et al.*, 1990). In addition, it has been shown that selenium, a related metal, inhibits the methylation of arsenic in vitro (Styblo *et al.*, 1996). The role of diet and environmental factors in arsenic methylation can be studied in animals where these factors can be manipulated. Such studies would be useful in the design of epidemiological studies to determine the influence of dietary and nutritional factors on the capacity for arsenic methylation.

Characteristic modifiers include variation in susceptibility within the human population reflective of genotypic differences. Other characteristic modifiers include age of the individual exposed (e.g., children, elderly, pregnant women), gender differences and whether an individual is predisposed to susceptibility due the co-occurrence of another disease. Evaluation of arsenic metabolites excreted in urine from chronically exposed individuals suggest that there may be differences in the pattern and extent of arsenic methylation among the human population. Such differences could reflect genetic polymorphisms for the enzymes involved in arsenic methylation. Polymorphisms for enzymes that catalyze other methylation processes have been observed (Weinshilboum, 1989). Its also been observed that some nonhuman primates have limited or no methylation capacity (Vahter and Marafante, 1985; Vahter *et al.* 1995).

In addition to the above potential modifiers, there is evidence suggesting that arsenic is an essential trace element for goats, chickens, minipigs, and rats (NRC, 1989). However, no comparable data are available for humans, and conclusive demonstration of arsenic essentiality in humans is hampered by the lack of a postulated mechanism. The possibility of arsenic as an essential element could affect the interpretation of arsenic risk at low-doses.

Ongoing EPA Research

Current research is being conducted by EPA to evaluate the impact of micronutrient status on arsenic metabolism and toxicity. In addition, studies are being completed on the preventive effects of zinc, selenium and antioxidants on arsenic induced malformations in rodent embryos. Results from these studies can be used in the evaluation of dose response relationships for arsenic induced toxicity and carcinogenicity.

III.6 Proposed Health Effects Research

Proposed research topics and current activities are summarized in Tables III-1 and III-2.

Effects Issue 1. What are the Health Effects and Dose Response Associated with Arsenic Exposure?

1a. Conduct feasibility study on important health endpoints resulting from arsenic exposure.

This research will determine the feasibility of conducting an epidemiologic study in the U.S. or other appropriate populations focusing on important health endpoints. Further research, for example, on the incidence of internal cancers, reproductive, dermatologic and cardiovascular effects would provide the data necessary to determine dose response relationships at low arsenic doses and quantify the corresponding risks. Research in this area would be used to determine if the conduct of a full scale epidemiology study in the U.S. or other location would reduce the uncertainty in the existing risk assessment. High priority; intramural and extramural tasks

1b. Directed epidemiologic research on the health effects associated with arsenic exposures

(i) To address uncertainties associated with the current risk assessments for arsenic, this research would build upon ongoing studies of appropriate study design to evaluate the human health effects of arsenic at low doses and determine the dose response relationship for important health effects attributed to arsenic exposure. This research would expand the scope of ongoing studies in Chile and India, for example, in order to estimate the level of

exposure to individuals and follow these individuals over a period of time. Since this research builds on existing studies, it could be completed in the near term.

(ii) In the longer term, a full scale epidemiologic study would be designed based on the results of the feasibility study (see 1a). This study would be developed in areas where exposures could be well defined and the range of exposure broad. These studies are long term in design and would be resource intensive. This research might be developed through or in collaboration with other groups such as the National Institutes of Health or the World Health Organization on study design and data analysis.
High Priority, if feasible; intramural and extramural task

1c. Research on important health endpoints in animals

This research would complement epidemiologic investigations concerning the health effects and dose response analysis of arsenic exposures. This research would include evaluations on developmental, reproductive, cardiovascular, neuro- and other endpoints. Use of animal models may enable this question to be answered more easily or practically than human studies. Research in these areas should combine *in vitro* and *in vivo* techniques in animals to determine dose response to further characterize the toxicity of various arsenic species and help target endpoints for study in epidemiologic studies.
Medium priority; intramural and extramural task.

Effects Issue 2: What are the Dose Responses for Various Effects at Low Doses?

2a. Develop biomarkers of effect and susceptibility

Use of biomarkers can help reduce uncertainty in the interpretation of epidemiologic studies and provide insights into the shape of the dose response curve, and mechanism of action. Biomarkers such as hyperkeratoses and chromosomal mutations in human blood cells may provide insight into such factors such as human variability and potential susceptibility to arsenic toxicity. These studies would further develop biomarkers like the blood chromosomal aberrations or DNA methylation to be used as measures of biologic effect and susceptibility. This research would develop and evaluate additional biomarkers of effect for use in epidemiologic studies. Development of this tool could facilitate the development

of a human pharmacokinetic model and improve our understanding of dose response relationships for estimating risk.
High priority; intramural task.

2b. Research for development of a PBPK model

Refinement of a PBPK model (and the studies necessary for model development) for arsenicals would provide a better understanding of the metabolism and relevant target tissues subject to arsenic toxicity. Included in this area are studies that would characterize arsenic metabolism in humans and improve mass balance data on typical human metabolism of arsenic at various doses, by different routes of exposure and with different chemical forms. Development of a PBPK model may help reduce uncertainty in the arsenic risk assessment for cancer and noncancer effects.
High priority; intramural and extramural task.

2c. Develop laboratory model systems to understand mechanisms of arsenic toxicity and carcinogenicity

This research would encompass the development of laboratory model systems such as an animal model utilizing transgenic mice or other appropriate organisms or promotional systems. In order to understand how arsenic causes cancer or other toxic effects, it may be useful to develop a model system. This model system might then be used to generate hypotheses concerning the molecular mechanism of carcinogenesis and toxicity in humans. Understanding the mechanism can often be used to identify biomarkers that would be useful for developing dose response relationships, including possible threshold effects, for detecting human populations sensitive to arsenic. A better understanding of the mechanism of action for arsenic induced carcinogenicity and toxicity can lead to the future development of a biologically based dose response model for arsenic.
High priority; intramural and extramural task.

2d. Determine mechanisms by which arsenic causes cancer and noncancer effects

This research will utilize *in vitro* and *in vivo* techniques to evaluate mechanisms for cancer and noncancer effects induced by arsenicals. Mechanistic research further refines the link

between exposure and effect. Areas for investigation include: enzymology of arsenic methylation; action of arsenicals in multistage carcinogenesis or as tumor promoters; mechanistic basis of alteration of DNA methylation by arsenic; identification of the human arsenic methyltransferase gene; effects on methyl dependent recombination repair, and investigation of noncarcinogenic mechanisms of action. The results from these studies may provide insights regarding the mode of action for arsenic and assist in the low-dose evaluation in arsenic risk assessment.
High priority; intramural and extramural task.

Effects Issue 3: What are the Modifiers of Susceptibility and Dose Response?

3a. Factors that affect human susceptibility

Arsenic metabolism involves a complex series of oxidative and reductive processes that can be affected by a variety of factors such as diet, genotype and health of the individual. Given the critical role of methylation in the disposition of arsenic, further characterization of the enzymatic basis for arsenic methylation is needed. At present, arsenic methyltransferase in humans has not been isolated, but transferases in general are polymorphic. Understanding the factors affecting human sensitivity would improve arsenic risk assessment. The objective of this study would be to evaluate the variations in arsenic metabolism as reflected in variations in urinary metabolites or other biomarkers of exposure that are associated with the exposure level, nutritional status, including potential essentiality of arsenic, genetic factors, and other variables. There is a need for the development and refinement of assay procedures to characterize arsenic methyltransferases in human tissues. In addition, the study would compare biomarkers of arsenic metabolism in individuals exposed to varying levels of arsenic with differences that include nutritional status, age, sex, and genetic variations. This research may involve epidemiological studies, human clinical studies, or animal studies. Research results would help characterize human variability in sensitivity to arsenic exposure and potential mechanisms of action.
High priority; intramural and extramural task.

TABLE III-1: EFFECTS RESEARCH STRATEGY MATRIX FOR ARSENIC

ISSUE	TASK	PRODUCT	USE
EFF. Issue 1. What are the health effects and dose response associated with arsenic exposure?	1a. Determine feasibility study on important health endpoints for carcinogenic effects for epidemiologic studies. High Priority	Determination if epidemiologic study with improved design is feasible.	Determine health endpoint and dose response for use in full scale epidemiologic study.
	1b. Directed epidemiologic research on arsenic health effects utilizing ongoing studies or following outcome of feasibility study High Priority, if feasible	Epidemiology studies that determines relationship (linear or nonlinear) between arsenic exposure and effect.	Basis for improved risk assessment and derivation of MCL.
	1c.Research on important health endpoints in animals. High Priority	Results from animal studies on developmental, reproductive, cardiovascular, neuro- and other endpoints of arsenic toxicity.	Determine appropriate endpoint for future study design and serve as basis for risk assessment.
EFF. Issue 2 What are the dose-responses for various effects at low doses?	2a. Develop biomarkers of effect and susceptibility High Priority	Biomarkers to assess biologic effect and susceptibility	Standardize protocol for assessing exposure and utilize tools for improving the precision of the risk assessment.
	2b. Research to support refinement of a PBPK model High Priority	Relevant species-specific parameters for development of PBPK model.	Incorporation into PBPK model (RA task 1a).

ISSUE	TASK	PRODUCT	USE
	2c. Develop laboratory model systems to assess mechanism of arsenic induced carcinogenicity and toxicity. High Priority	Animal model utilizing transgenic mice or other appropriate organism or model system.	Understand cause and effect relationship between arsenic exposure and effect.
	2d. Determine mechanisms by which arsenic exerts it's carcinogenic and noncarcinogenic effects. High Priority	Results from in vitro and in vivo studies on mechanisms of arsenic-induced carcinogenicity and toxicity.	Reduce uncertainty in low-dose extrapolation in arsenic risk assessment.
EFF. Issue 3. What are the modifiers of susceptibility and dose response?	3a. Factors that affect human susceptibility High Priority	Method for assessing arsenic metabolism capacity in humans.	Necessary component of PBPK and BBDR models, and improve understanding of human susceptibility.

TABLE III-2: EFFECTS TASK SUMMARY, CURRENT ACTIVITIES AND PROPOSED SEQUENCE FOR STUDIES

	Task Type[1]		On-going	Priority	TIME FRAME[2]					
Task - Short Study Title	**I**	**E**	**Y/N**	**Priority**	**FY97**	**FY98**	**FY 99**	**FY00**	**FY01**	**FY02**
Task 1a. Feasibility study on important health endpoint (Utah cohort; feasibility study)	I	E	Y	High	EPA	EPA	EPA			
Task 1b. Directed epidemiology study (i) - ongoing study collaboration (Chile, India)	I	E	Y	High	EPA	EPA				
Task 1b. Directed epidemiology study (ii) - long term development	I	E	N	High if feasible				X	X	X
Task 1c. Research on important health endpoints in animals.	I	E	N	Medium		X	X	X		
Task 2a. Develop biomarkers of effect (Urinary Metabolic Profile)	I		Y	High	EPA	EPA				
Task 2b. Refinement of PBPK model	I		Y	High	EPA	EPA	EPA	EPA		
- Biomethylation and disposition of arsenic	I		Y	High	EPA	EPA	EPA	EPA		
- Determine toxicodynamics of arsenic in mice	I	E	N	High		X	X	X		

1 I=Intramural (EPA inhouse research), E=Extramural (EPA sponsorship through grant or coop)

2 EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort

X = EPA resources insufficient to address these tasks, need external research effort

Task - Short Study Title	I	E	Y/N	Pri-ority	FY97	FY98	FY 99	FY00	FY01	FY02
Task 2c Develop laboratory model systems for arsenic mechanistic evaluation - P53 deficient mice	I		Y	High	EPA	EPA	EPA			
Task 2d. Arsenic mechanism - Arsenicals, oxidoreductases, and cellular redox status	I		Y	High	EPA	EPA	EPA	EPA		
- arsenic mechanism (Enzymology of arsenic methylation)	I		Y	High	EPA	EPA	EPA	EPA		
- arsenic mechanism (Action of arsenicals in multistage carcinogenesis)	I		Y	High	EPA	EPA	EPA	EPA		
- arsenic mechanism (Mechanistic basis of alteration of DNA methylation by arsenic)	I		Y	High	EPA	EPA	EPA	EPA		
- arsenic mechanism (Identification of human arsenic methyltransferase gene)	I	E	N	High		X	X	X		
- arsenic mechanism (Arsenic perturbation of cell cycle and induction of cell death in embryos)	I		Y	High	EPA	EPA	EPA	EPA	EPA	EPA
Task 3a. Impact of micronutrient status on arsenic metabolism and toxicity	I		Y	High	EPA	EPA	EPA			
- Impact of macronutrient status on arsenic metabolism and toxicity	I	E	N	High		X	X	X		
- Variation of arsenic metabolism in humans	I	E	N	High		X	X	X		
- Polymorphisms of the human arsenic methyltransferase gene and variation in susceptibility	I	E	N	High		X	X	X		
- Prevention of arsenic induced malformations by antioxidants, selenium and zinc	I		Y	High	EPA					

CHAPTER IV
RISK MANAGEMENT RESEARCH FOR ARSENIC IN WATER

IV.1 BACKGROUND

Uncertainty about cancer and noncancer risks in populations exposed to low levels of arsenic in drinking water is one of the main driving forces in this Research Plan. When EPA requires regulations to protect humans from harmful exposure to low doses of arsenic in drinking water, there must be effective treatment and control technologies in place capable of achieving the regulated limits. Therefore, besides investigating exposure, mechanisms of action and epidemiology; treatment options capable of acceptable arsenic control must be identified and tested. The goal of this part of the Plan is to assure that the desired final drinking water arsenic concentration be technically achievable, the control technology(ies) reliable and cost effective, while not significantly increasing residual management problems. At this time one cannot state with certainty that the known arsenic control technologies will function effectively if lower arsenic levels are promulgated. Additional data are needed to determine the effectiveness of arsenic treatment and control. In the pursuit of an achievable arsenic standard, EPA must also be mindful not to adversely impact the treatment of other water quality parameters, but to build on those technologies wherever possible.

Arsenic exists in water supplies as several chemical species usually encompassing two oxidation states (arsenic III and arsenic V) with arsenic (V) being more easily removed. The common soluble species of arsenic (V) are forms of arsenic acid: H_3AsO_4, $H_2AsO_4^{-1}$, $HAsO_4^{-2}$ and AsO_4^{-3}. The common soluble species of arsenic (III) are: H_3AsO_3 and $H_2AsO_3^{-1}$. In the pH range of 5 to 9, equilibrium data indicate that the predominant arsenic (V) species will be $H_2AsO_4^-$ and arsenic (III) species will be H_3AsO_3. In addition to soluble arsenic species, there is increasing evidence (Chen, et al., 1994; Hemond, 1995) that particulate arsenic is a common constituent in the water supplies. A recent arsenic survey (Edwards, et al., in press) of domestic water systems showed significant levels of particulate arsenic, averaging 17% of the total. A third component for drinking water arsenic could be organically bound, but levels reported on this component were rarely greater than 1 µg/L (Anderson and Bruland, 1991). For this analysis only soluble inorganic arsenic and particulate arsenic will be considered as the species requiring control.

A number of control technologies can remove arsenic: coagulation/filtration (CF), lime softening (LS), activated alumina (AA), ion exchange (IE), reverse osmosis (RO), nanofiltration (NF) and electrodialysis reversal (EDR). These technologies have been applied to water supplies containing arsenic and demonstrated to work. A new, lower MCL would push the required

performance beyond reported levels opening up areas of uncertainty in performance, reliability and impact on other treatment operations.

Historically, the level of treatment chosen for arsenic has been closely correlated to the MCL of 50 µg/l. Improvements in analytical techniques plus the statutory requirements in the SDWAA of 1996 may establish a substantially lower limit. If the MCL for arsenic is lowered, a parallel evaluation of available treatment technology capability must also be carried out to document required performance and/or identify areas where additional research is necessary.

IV.2 State of the Science for Arsenic Control

How Effective are Available Technologies for Meeting a Lower Arsenic MCL?

As discussed above, there are numerous treatment technologies that can be brought to bear on removing arsenic from drinking water. The AWWARF Research Needs Report (1995) and Malcolm Pirnie's Report on Treatment and Occurrence of Arsenic in Potable Water Supplies (1993) indicate that little is known about the performance of these processes for treatment of arsenic concentrations in the less than 50 µg/L range. The key risk management issues are (1) what are the performance limitations on treatment technologies that could be applied for arsenic control, and (2) how does this treatment impact small systems, and (3) what impact is there on the management of process residuals?

Table IV-1 shows the performance of seven arsenic control technologies, which meet the 50 µg/L MCL. Table IV-1 also projects the level of performance that may be required of these technologies if the MCL is lowered. In some instances, control technologies have performed efficiently and approached a concentration that might be expected under a more stringent MCL, but in the overwhelming number of cases the required performance was not documented. Performance data gaps exist and the proposed research under this Plan would address those gaps by: collaborating with existing studies, conducting independent performance studies, and initiating basic research on arsenic's interactions with chemicals/additions.

AWWARF is presently conducting arsenic treatment removal efficiency research for lime softening and coagulation/filtration. A significant amount of performance data will be collected and will reduce some of the uncertainty associated with arsenic control. Because arsenic-containing groundwater varies in composition, it would be prudent for EPA to investigate additional water

quality parameters before casting final judgement on lime softening and coagulation/filtration. Adsorptive media and membranes are also being studied, but using a fairly high natural organic material raw water (Total Organic Carbon ≈ 3 mg/L) which is not representative of most ground waters. Since ground water systems are the most likely candidates for the adsorptive technologies like activated alumina, research would be required to determine key performance and cost factors for a source water with lower Total Organic Carbon. The proposed research in this Plan would build on, augment, and validate the arsenic control data available, generate additional treatment information and advance the understanding of the control technologies necessary to achieve a new arsenic standard for drinking water.

The regulation of arsenic by a more stringent MCL may impact other treatment operations. In some cases, a specific oxidation step in the treatment process will need to be added, to optimize removal efficiency, but in others, optimization of existing unit processes like softening or filtration may be sufficient to improve arsenic control . While researching the performance aspects of arsenic control, this research effort will also look at the entire water treatment system and make recommendations on leveraging existing options for arsenic control.

Are There Cost Effective Technologies for Small Systems?

Small water supply systems (<10,000 customers) pose special problems for regulation and a change in the arsenic MCL could cause significant operational/compliance problems for these systems. Table IV-1 illustrates the arsenic removal gap that exists between current control technologies and the projected future need. In some cases the optimization of the control technique may be technically insufficient or too costly for a small system to implement. In situations where technology or economics fail, alternative compliance approaches must be developed.

How Can the Residuals be Effectively Managed?

While the treatment of source water for arsenic removal has been widely documented, efficiency, reliability and cost effectiveness are topics slated for additional research. The improved treatment efficiency will produce a residue with elevated arsenic concentrations, which might affect disposal options and cost of residual management . Residues subjected to the toxicity characteristic leaching procedure (TCLP) are a characteristically hazardous waste due to arsenic if the TCLP extract contains 5 mg/L arsenic. The TCLP procedure defines a TCLP hazardous waste as producing an extract containing greater than 100 x the referenced MCLs of specified chemicals. Lowering the MCL for drinking water might initiate a new regulatory requirement under the

Resource Conservation and Recovery Act (RCRA) in which case the TCLP arsenic trigger value will also be lowered. Thus, the strengthening of the arsenic drinking water MCL could have a multiple regulatory impacts on a utility and contribute to unfavorable economics for various arsenic removal technologies. All of the research projects initiated under this plan will require residuals management to be an evaluation factor with recycling of active arsenic removal media being a priority. If recycling is not a technical option, the minimization of the volume of arsenic containing sludges and the degree of arsenic mobility will be a research topic.

Ongoing EPA Research

The ongoing work involves evaluating ion exchange and coagulation-microfiltration technologies for removal of arsenic from ground water. Successful laboratory experiments led to a field study and the testing of different ion exchange resins. Treated arsenic levels were reduced to less than 2 µg/l and maintained this level for extended treatment times.

IV.3 Risk Management Research

The reliable control of arsenic at levels below 50 µg/L by currently available treatment technologies has not been completely demonstrated. In addition to the overall performance problem there are special technical and economic concerns raised by application of arsenic control to small drinking water systems. Thirdly, additional arsenic removal from drinking water may result in an enriched residual and possibly generating a new regulated waste stream.

Risk Management Issue 1 (RM 1). How Effective are Available Technologies for Meeting a Lower Arsenic MCL?

RM 1a. Laboratory and Field Testing on Different Arsenic Control Technologies

A reduction in the MCL for arsenic in the near future is going to require that control technology be capable of meeting the technical requirements of the revised limit. There are about seven different types of control technology applicable to arsenic control and a significant amount of performance/reliability work has been completed. The main focus of this research has been on surface waters with high levels of TOC. The research conducted in RM 1a. will survey the needs and gaps identified by past work and verify the performance of arsenic control technologies. The research carried out under RM 1a. will center on ground waters with low TOC values, and more of the mineral

characteristics associated with arsenic containing sources. The SDWAA of 1996 call for promulgation of a new arsenic MCL and this research directly supports that requirement by determining the availability of reliable control technologies.
High Priority for activated alumina, ion exchange, Medium Priority for Reverse Osmosis, Nanofiltration, and Electrodialysis Reversal

Risk Management Issue 2 (RM 2). Are There Cost Effective Technologies Available for Small Systems?

RM 2a. Cost Evaluations for Laboratory and Field Testing of Arsenic Control Technologies

Small drinking water treatment and distribution systems pose several additional challenges to regulators. The economic impact of a lower MCL for arsenic could be significant. As part of the technical evaluation for the various arsenic treatment technologies studied in RM 1a., the economics of each tested system will also be evaluated using existing OW cost equations and models. Applicability of the control technologies to point of use (POU) considerations will also be part of the technical/economic evaluation.
Medium Priority

Risk Management Issue 3 (RM 3). How can Residuals From Arsenic Control be Managed Most Effectively?

RM 3a. Arsenic Control Residual Management

A reduced MCL for arsenic will result in the enrichment of process residual material. The disposal of this material may also be impacted by a lower arsenic TCLP value and trigger regulation under RCRA. Residuals associated with RM 1a. and other arsenic removal projects will be evaluated for arsenic content and mobility with emphasis being on reducing the environmental impact of its disposal. Residuals are important from a total arsenic management standpoint, and have not received sufficient attention in past studies.
High Priority

Table IV-1+
Arsenic Control Technology Performance (100 µg/l Influent)

Technology	Performance* Currently Required, %	Reported Treatment Performance, %	Projected** Performance Needed, %
1. Coagulation Filtration	50	90 to 99	98
2. Lime Softening	50	40 to 99	98
3. Activated Alumina	50	43 to 94	98
4. Ion Exchange	50	75 to 96	98
5. Reverse Osmosis	50	96 to 99	98
6. Nanofiltration	50	95 to 98	98
7. Electrodialysis Reversal	50	Not reported	98

+Adopted from Malcolm Pirnie, 1993

*Based on current MCL of 50 µg/l

**Based on treatment requirements significantly less than 50 µg/l

TABLE IV-2. RISK MANAGEMENT RESEARCH STRATEGY MATRIX FOR ARSENIC

ISSUE	TASK	PRODUCT	USE
RM Issue 1 How Effective are the Available Arsenic Treatment Technologies for Meeting a Lower MCL	RM Task 1a. Conduct Laboratory and Field Tests on Different Arsenic Control Technologies. High Priority (AA, IE) Medium Priority (NF, RO, ER)	Series of Reports describing the technical performance of the different arsenic control technologies	Will be used in the rule making process to demonstrate the capabilities and performance of arsenic control technologies
RM Issue 2 What are the Technical and Economic Considerations of Arsenic Control for Small Systems	RM Task 2a. Complete Cost Evaluations for all Arsenic Control Technologies Tested in RM 1a. Medium Priority	Series of Reports describing the economic considerations associated with the operation of each treatment technology studies in RM 1a.	Will be used to determine any adverse economic considerations that will arise from small systems complying with the revised MCL for arsenic
RM Issue 3 How can Arsenic Enhanced Residuals be Effectively Managed	RM Task 3a. Conduct a Study on the arsenic characteristics of the residual material generated by testing in RM 1a. High Priority	A series of reports outlining the composition of the residual arsenic and its mobility	Used to determine the recycle\ disposal options for the residual material generated by the technologies tested in RM 1a.

TABLE IV-3: RISK MANAGEMENT TASK SUMMARY, CURRENT ACTIVITIES AND PROPOSED SEQUENCE FOR STUDIES

	Task Type[1]	On-going	Priority	TIME FRAME[2]					
Task - Short Study Title	**I**	**E**	**Y/N**	**Priority**	**FY97**	**FY98**	**FY99**	**FY00**	**FY01**	**FY02**
RM Task 1a. Bench/Field Testing of Arsenic Control Technologies	I	E	Y	High for AA & IE Medium for NF, RO & ER	EPA	EPA	EPA			
RM Task 2a. What are the Technical and Economic Considerations of Arsenic Control for Small Systems?		E	N	Medium	EPA	EPA	EPA			
RM Task 3a. How Can Arsenic Enhanced Residues Be Effectively Managed?		E	N	High	EPA	EPA	EPA	EPA		

1 I=Intramural (EPA inhouse research), E=Extramural (EPA sponsorship through grant or coop)

2 EPA = EPA has ongoing studies or plans to address this task in future years; some tasks may require additional research beyond EPA's planned effort

X = EPA resources insufficient to address these tasks, need external research effort

NOTE: RM Tasks 2a. and 3a. are to be carried out as subtasks under the technology performance research in RM Task 1a.

CHAPTER V
OVERALL PRIORITIES IN ARSENIC RESEARCH

The preceding chapters have presented research options and priorities for arsenic. Each chapter focused on a particular aspect of the standard risk assessment/risk management paradigm and associated research needs. Accordingly, the chapters did not always provide a global perspective on the total plan.

A series of Tables were developed for this chapter in order to assist the reader in forming a comprehensive picture of the arsenic research plan. Tables dealing with research initiatives on the following topics are included:

- Analytical Methods
- Exposure Assessment
- Metabolism/ Biomarkers/PBPK Model Development
- Health Effects and Dose Response
  - Cancer endpoints
  - Noncancer endpoints
- Mechanisms of Action
- Human Susceptibility Characteristics
- Potable Water Treatment Modalities

The Tables integrate the various components of the research plan; they illustrate the importance of specific research opportunities, interaction of components of the plan and limitations on what can reasonably be accomplished in a limited time span. Each table highlights the contributions of the proposed activity to the arsenic risk assessment, presents a priority for the activity and targets a time frame for its accomplishment. The projected responsibility for ORD is also delineated.

1. Research Priorities for Arsenic: Exposure Research - Methods

Research issue	Research opportunities*	Contribution to risk assessment	Issues/limitations /links
Refinement of analytical methods. The species specific toxicity of arsenic requires the utilization of speciation based analysis to accurately quantify the risk associate with primary exposure route (i.e., drinking water and dietary ingestion of arsenic) Methods are required to extract, separate and quantify arsenic compounds in a wide variety of biological and dietary samples to support this risk assessment. To date, validated analytical methods, similar to those used in compliance monitoring do not exist.	Speciation based methodologies are needed in biological samples (i.e., urine and blood) and dietary ingestion samples (i.e., duplicate diet and targeted food items). The separation of the valence states of inorganic arsenic may be a consideration in treatment related issues. Biological Samples: The separation of inorganic arsenic (As(III) and As(V)), MMA, DMA and arsenobetaine is important in pharmacokinetic, mechanistic, biomarkers and bioavailability studies. The analytical methodologies must address sensitivity issues in urine and blood while providing species specific integrity. Biological tissue will require unique extraction procedures prior to analysis. Dietary Samples: A reliable extraction and speciation analysis procedure for inorganic and organic arsenicals is required to address the relative source contribution of arsenic dietary ingestion. The primary concern will be the separation of inorganic from organic arsenic with specific applications requiring a more complete speciated analysis. Tasks: EXP 1a – 4c	Speciation based analytical methods are needed to accurately quantify the risk associated with exposure routes which contain both organic and inorganic arsenic. The relative source contribution of diet to arsenic exposure needs to reflect a speciation based analysis. Analytical methods development can support a range of pharmacokinetic, mechanistic, biomarker and bioavailability studies to obtain a better understanding of the biological processing of arsenic.	Methods for the analysis of arsenic in drinking water were not identified as a high priority, since such analysis is unlikely to significantly affect the risk assessment and risk management decisions. However, analytical techniques which aid in the assessment of relative source contribution of dietary ingestion, aid in treatment evaluation, identify biomarkers, aid in pharmacokinetic and mechanistic studies require a speciation based methodology which is applicable to diverse and complex matrices.

Significance for risk assessment/Overall priority	Time frame/ORD role
Dietary arsenic exposure in the U.S. is a component of understanding cumulative arsenic risks from drinking water and food. Pharmacokinetic and mechanistic work to better understand the physiological processing of arsenic and its toxicological activities require speciation based analytical data in biological matrices. Priority: High	Near- to mid-term (1-5 years) for methods development. Research should be coordinated with other organizations such as FDA, USDA and CDC.

* Under research opportunities, task numbers reference proposed research in the Risk Assessment (RA), Exposure (EXP), Health Effects (EFF) and Risk Management (RM) chapters.

2. Research Priorities for Arsenic: Exposure Research - Background Exposures

Research issue	Research opportunities	Contribution to risk assessment	Issues/limitations /links
Background levels of arsenic exposure in the U.S. population Aside from drinking water, the diet is the primary source of exposure to arsenic for the general U.S. population. Intake and bioavailability of arsenic requires additional research.	Duplication diet sampling (collection of total dietary samples for individuals in a study groups) and market basket sampling (collection of representative food product samples from retail markets) are both useful approaches. Data on contributions of individual foods and/or food groups to arsenic intake is important . The bioavailability of arsenic species may be influenced by complex food matrices. Human bioavailability data are needed for determining uptake of dietary arsenic. Tasks: RA 2c; EXP 5a, 6a, 8a	Better knowledge of dietary inorganic arsenic exposure would provide perspective on the relationship between dietary arsenic and arsenic from drinking water. This information will be useful for risk characterization, as low-dose risk estimates should be considered in the context of arsenic exposure. For example, cumulative inorganic arsenic exposure will need to be considered in margin of exposure comparisons. There is substantial information on total arsenic in the U.S. diet and limited information on inorganic arsenic.	Methods development will be needed for measuring inorganic arsenic in the diet. Relevant methods for assessing bioavailability need definition. Mass balance studies of arsenic absorption, distribution and excretion will support bioavailabiltiy determinations.

Significance for risk assessment/Overall priority	Time frame/ORD role
This research will support refinement (verification or change) of current estimates of inorganic arsenic intake in the diet. It will provide improved data for the relative source contribution in the risk assessment. Priority: Medium/High	Short to mid term (2-5 years) Data could be collected relatively rapidly if sufficient resources and analytical methods are available. Need to work with FDA and USDA.

3. Research Priorities for Arsenic: Linking Exposure and Effects Research

Research issue	Research opportunities	Contribution to risk assessment	Issues/limitations /links
Metabolism, PBPK models and biomarkers of exposure	Data on absorption distribution metabolism and excretion are needed to quantify the concentration and species of arsenic present at target tissues. Opportunities exist to conduct studies in populations that have significant environmental exposure. Mass balance data from humans will be needed for PBPK model development. Biomarkers of exposure will help correlated exposure data with observed health effects. Urine and blood arsenic have been identified as useful biomarkers of recent exposure. Hair and nail arsenic reflect longer tern exposures. Other endpoints such as methylation of DNA have been suggested as biomarkers of both exposure and effect but require quantification and validation. Excretory products will help elucidate metabolic processing and pathway saturation. Tasks: RA 1a, 2a, 2b; EXP 7a, 8a; EFF 2a, 2b.	Researchers hypothesize that saturation of arsenic metabolism may affect the dose response relationship although available data suggest that metabolic processes are substantially similar over a broad dose range. Analytical and logistical issues complicate the quantification of arsenic exposure from multiple sources. If a simple biomarker could be correlated to total exposure it would be of great value in risk assessment.	Mass balance studies will address bioavailability of arsenic from the diet. Analytical data are needed to speciate and quantify human environmental exposures and tissue exposures. Blood and urine are very limiting as biomarkers because they only reflect recent exposures, demand frequent sample collection and are labor intensive. Information on other biomarkers with longer half lives will contribute to an understanding of mechanism of action and pharmacokinetics.

Significance for risk assessment/Overall priority	Time frame/ORD role
Validated, practical biomarkers of long term arsenic exposure would contribute to exposures assessment and epidemiological research. Absorption, distribution, metabolism and excretion data are required of PBPK modeling. Will help answer question regarding saturation of arsenic metabolism. Provide data for pharmacokinetics modeling Priority: Medium/High	Medium for data collection and interpretation; longer term for model development and verification. Appropriate for ORD sponsorship

4a. Research Priorities for Arsenic: Effects Research - Cancer Endpoints

Research issue	Research opportunities	Contribution to risk assessment	Issues/limitations /links
Determine cancer endpoints and dose response associated with arsenic exposure	A number of health effects in human and animals are attributed to arsenic in drinking water. Research in Chile, India, and Taiwan are evaluating arsenic induced internal cancers. Data from these ongoing studies can be used to determine dose response at low doses. In the long term, a feasibility study in the US is underway to determine the potential for a full scale study of cancer and important noncancer health endpoints. Studies in animals may facilitate and evaluation of other endpoints and compliment human studies. Tasks: RA 1c; EFF 1a, 1b, 1c.	Internal cancers induced by arsenic are probably the health endpoint of concern; however, cardiovascular and reproductive/ developmental are not as well characterized. Dose response models for these endpoints would be considered as the basis for arsenic risk assessments and regulatory decisionmaking.	Strengthening exposure data in ongoing studies and future epidemiologic studies is needed. This will require close collaboration and cooperation with the principal investigators. Utilization of biomarkers may facilitate exposure and effects analyses.

Significance for risk assessment/Overall priority	Time frame/ORD role
Provides information on health endpoints and dose response at low doses of arsenic exposure. This area is a source of uncertainty in the current arsenic risk assessments. Results from ongoing studies are expected in the near term and could be used to refine existing risk assessments for arsenic. Priority: High if feasible	Applying data from ongoing studies in a dose response analysis could be completed in the short term (1-3 yrs). This research could be completed by EPA. The feasibility study and full scale study is an area of long term research that will require collaboration with non-EPA organizations with results not expected for more than 5 yrs.

4b . Research Priorities for Arsenic: Health Effects

Research issue	Research opportunities	Contribution to risk assessment	Issues/limitations/links
Noncancer Effects. Limited data indicate that health effects other than cancer may present significant health concerns for arsenic. Vascular damage has been noted in diverse studies and is a potentially important issue for the US population because of the high background rate for cardiovascular disease. Neurological effects from arsenic have been noted in a drinking water study with a US population. Dermatological abnormalities (hyperkeratosis and other effects) have been extensively documented to result from arsenic exposure. These effects form the basis for EPA's current RfD for arsenic, but dose response data are lacking. Potential developmental effects from arsenic have also been identified.	Generate epidemiological data on arsenic's non-cancer health effects. Dose response data on non-cancer effects would be particularly valuable in supporting arsenic risk conclusions. There is a significant opportunity to conduct dose response studies of hyperkeratosis in suitable human populations. Hyperkeratosis occurs more frequently that skin tumors in persons exposed to arsenic, allowing generation of response data at lower exposure levels. Animal toxicity studies can provide insight into the hazard and dose response for non-cancer toxic effects, such as vascular, neurological, and developmental effects, provided that the animal models are relevant to humans. Tasks: RA 1b, 2b; EFF 1a, 1b, 1c	Data to evaluate risks from non-cancer effects of arsenic exposure are limited. Additional data on the occurrence of these effects, preferably including data on dose response or the occurrence of effects at lower dose levels, can fill a significant data gap. Hyperkeratosis is strongly indicated as a precursor of skin tumors; refinement of the dose response for this endpoint may enable it to be used as a surrogate in consideration of the skin cancer dose response.	Priority should be placed on seeking opportunities for add-ons to ongoing epidemiological studies. Cooperative efforts can support improved dose-response information and occurrence data for non-cancer endpoints. The feasibility of conducting significant new epidemiological studies in relevant US or international populations should be assessed, with attention to ability to generate adequate exposure and effects measures. A longer term priority is new epidemiological studies. Where animal research is undertaken, similarities and differences in animal and human response need to be integrated in the design and interpretation of studies to insure relevance.

Significance for risk assessment/Overall priority	Time frame/ORD role
Data on the noncancer health effects of arsenic may have important impact on the overall heath risks from arsenic. Documentation of a risk of hyperkeratosis at doses below those associated with cancer may provide significant support for the weight of evidence cancer risk assessment. Priority: High	Limited add-ons to existing studies may be completed on a short term basis, while substantial new epidemiological studies are probably long term in nature. It is appropriate to expend ORD's limited resources in support of studies of limited scale.EPA needs to seek cooperative relationships with other agencies to support substantial new studies.

5. Research Priorities for Arsenic: Mechanisms of Toxicity

Research issue	Research opportunities	Contribution to risk assessment	Issues/limitations /links
Mechanisms of toxicity	Current research suggests a number of promising approaches that may aid in understanding arsenic toxicity. There is potential for studies with a wide range of experimental systems (biochemical, cell cycle, tissue culture, whole animal). These studies will look at a range of endpoints that may relate to arsenic toxicity (DNA damage, DNA methylation, initiation/promotion experiments/ oncogene studies, enzyme systems, enzyme kinetics, etc.) Tasks: RA 1a, 2a, 2b; EFF 2c, 2d	Provides insight into mechanisms that may influence to arsenic carcinogenesis and toxicity.	Multiple mechanisms for arsenic toxicity may be present. Tools to relate mechanistic risk to human risk need to be developed. Appropriate studies will relate mechanistic information to observed human toxicity. Work should be linked to studies of human susceptibility.

Significance for risk assessment/Overall priority	Time frame/ORD role
Potential for elucidating mode of action for arsenic. Could assist in the evaluation of low dose risks and susceptibility factors. Priority: High	Long term ORD laboratories will contribute to specific studies. ORD can fund related academic research.

6. Research Priorities for Arsenic: Modifiers of Susceptibility

Research issue	Research opportunities	Contribution to risk assessment	Issues/limitations /links
Modifiers of human susceptibility	Factors affecting human susceptibility include environmental and characteristic modifiers. Examples include diet or concurrent exposure to other toxins, genetic differences, age, gender, and preexisting disease. Epidemiologic or human clinical studies can provide insight on the influence of these factors on the incidence of effect in arsenic-exposed populations. In vitro or animal studies may also be conducted when human testing is not feasible or practical. Research on susceptibility factors can also provide insights on mechanisms for human toxicity. Tasks: EFF 3a	Identification of factors influencing human susceptibility to arsenic toxicity. This research may: 1)improve our understanding of human variability and sensitivity to the action of toxic agents, 2)identify potentially sensitive populations such as children, disease or nutritionally compromised individuals, 3) provide insight into mechanisms of action, and 4)help in the design of future epidemiology and toxicology studies.	This research requires measurable environmental or human characteristics that may relate to arsenic toxicity. A variety of susceptibility factors can be proposed. Research efforts will need to determine practical human endpoints or environmental conditions, consider costs and scientific merits. Where possible, research could be linked with ongoing studies. Close collaboration with principle investigators would be needed.

Significance for risk assessment/Overall priority	Time frame/ORD role
Potential for identification of sensitive subgroups with high susceptibility to arsenic toxicity. Presence or absence of susceptibility factors may have implications for risk management decisions. Potential for direct insight into mechanisms of action for arsenic toxicity which could aid in evaluation of low dose risks. Priority: High	Research could be completed in a 3-5 yr time frame through use of clinical and in vitro techniques and through application of data from ongoing studies. Additional research would be needed to evaluate effects of susceptibility factors on arsenic dose response. This research could be completed by EPA and possibly with collaboration with non-EPA organizations.

7. Research Priorities for Arsenic: Risk Management Research

Research issue	Research opportunities	Contribution to risk management	Issues/limitations/ links
Cost-effective treatment techniques for removing arsenic from drinking water The reliable control of arsenic at levels below 50 µg/L by currently available treatment technologies has not been adequately demonstrated. In addition, there are special technical and economic concerns associated with application of arsenic control to small drinking water systems.	Important research issues include: 1) Laboratory and field testing of different arsenic control technologies. Seven applicable arsenic control technology types need to be evaluated for performance and reliability. 2) Evaluating the cost effectiveness of the arsenic control technologies for small drinking water systems. 3) Determining effective management controls for residuals produced from arsenic control technologies. Tasks: RM 1a, 2a, 3a	This work will determine the feasibility of any new proposed arsenic MCL by determining BAT and the costs associated with arsenic controls, both in large and small drinking water systems.	Analytical methodology refinements in arsenic speciation will be needed for optimal determinations of control treatment technologies and for determination of risks from residuals using TCLP tests.

Significance for risk assessment/risk management and Overall priority	Time frame/ORD role
Provides critical information for EPA's determination of arsenic control BAT and the feasibility for reducing arsenic in drinking water supplies, especially in small systems. Priority: High (1 &#3) , Med (2)	Short- to mid-term (1-4 years) for determining cost effective control technologies and BAT feasibility. ORD will work closely with OW and outside entities, such as AWWARF, in conducting this research and determining feasibility.

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